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Parameters for Estimation of Casualties from Ammonia (NH3), Tabun (GA), Soman (GD), Cyclosarin (GF), and Lewisite (L)

Audrey C. Kelley
Carl A. Curling, Project Leader

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INSTITUTE FOR DEFENSE ANALYSES
4850 Mark Center Drive
Alexandria, Virginia 22311-1882

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About This Publication

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Executive Summary

The Institute for Defense Analyses (IDA) developed a symptom-based methodology, now promulgated as North Atlantic Treaty Organization (NATO) Standardization Agreement (STANAG) 2553, *Allied Medical Publication 8, NATO Planning Guide for the Estimation of CBRN Casualties* (*AMedP-8(C)*), to estimate the number, type, and timing of casualties from chemical, biological, radiological, and nuclear (CBRN) attack. Since the promulgation of *AMedP-8(C)*, IDA has performed additional analyses to extend the capabilities of the *AMedP-8(C)* casualty estimation methodology. These efforts include the addition of additional chemical and biological agents and models to incorporate the effects of medical treatment on the casualty estimate.

This paper describes the continued extension of the methodology to include five additional chemical agents that the Office of the Surgeon General (OTSG) specifically requested. The chemical agents are ammonia (NH_3), tabun (GA), soman (GD), cyclosarin (GF), and lewisite (L). It includes proposed model parameters without and with consideration of medical treatment for each agent, together with the derivation of those values. The paper supports transparency, reproducibility, and potential future refinement of the models by detailing the analytical choices made when determining parameters.

The intent is that the new models will be part of *Allied Medical Publication 7.5 (AMedP-7.5)*, which is currently in development at IDA and will eventually replace *AMedP-8(C)* in NATO doctrine.

Approach

Because the new models will be included in *AMedP-7.5*, they are designed to fit with it, rather than with *AMedP-8(C)*. The primary difference is in the chemical agent models. For the chemical agent, the physiological effects of the agent, the toxicity parameters available from sources, the new toxicity parameter estimates developed solely for this paper, and the generation of Injury Profiles, which map the progression of injury over time, are described. For each agent, the chapters include derivations and models for the "untreated" and "treated" case.

Summary of Proposed Model

The values proposed for each model were derived from extensive reviews of published literature. When raw data were available, these data were used directly to define original parameters or to independently verify values calculated elsewhere. When data

were limited, issues and gaps were identified, and strategies were developed to generate the best possible parameter values given the constraints.

For chemical agents, controlled human data are rare. Data from non-controlled human exposure (laboratory or industrial accidents) were plentiful for certain agents and were used where possible. Controlled studies with animal models, expert opinion, and comparison with similar agents also provided data for developing the model parameters.

Some context related to how *AMedP-7.5* will use the different parts of the chemical agent models is necessary. The median toxicity and probit slope (PS) will be used to estimate the number of individuals who will be binned into each Injury Profile cohort. The Injury Profile table shows how the severity of injury progresses over time, using the Injury Severity Scale defined in *AMedP-8(C)* and retained in *AMedP-7.5*. If the user chooses *not* to include the effects of medical treatment in the estimate, *AMedP-7.5* will output an estimate based on the Injury Profiles. If the user chooses to *include* the effects of medical treatment, *AMedP-7.5* will output an estimate based on the Injury Profiles and the medical treatment outcome reporting (MTOR) table.

Because the MTOR table focuses on reporting of casualties, some of its estimates are shifted 1 day later than the actual status change is estimated to occur. For example, Very Severe NH_3 casualties who are given medical treatment and do not survive are estimated to die 30 days after the attack. However, it is important for planners to know that on Day 1 to Day 30, the casualties would require hospital resources. Thus, the casualties would be reported by *AMedP-7.5* as wounded in action (WIA) from Day 1 to Day 30 and as having died of wounds (DOW) on Day 31

The following tables summarize the models. The body of this paper describes in detail the derivations of the proposed parameters.

Ammonia (NH_3)

Median Toxicities and PS for Inhaled NH_3

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	PS (Probits/Log(Dose))
NH_3 Very Severe	Lethal	67700	16.5
NH_3 Severe	Severe	7800	16.5
NH_3 Moderate	Moderate	1000	16.5
NH_3 Mild	Mild	350	16.5

[a] The median toxicity is an estimate for a 2-minute exposure.

Inhaled NH_3 Injury Profile

Time Point (Min)	NH_3 Mild	NH_3 Moderate	NH_3 Severe	NH_3 Very Severe
1	1	2	2	4
15	1	2	2	4[a]
60	1	2	2	
120	1	2	2	
180	1	2	2	
360	0	2	2	
720	0	2	3	
4320	0	0	3	
43200	0	0	0	

[a] Death is modeled to occur at this point.

NH_3 MTOR

Injury Profile	DOW	CONV	RTD
NH_3 Mild	0%	0%	Day 2: 100%
NH_3 Moderate	0%	0%	Day 4: 100%
NH_3 Severe	0%	0%	Day 8: 100%
NH_3 Very Severe	Day 31: 27%	Day 15: 36% Day 29: 37%	Day 91: 73%

Nerve Agents: Tabun (GA), Soman (GD), and Cyclosarin (GF)

Median Toxicities and Probit Slopes for Inhaled GA

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	PS (Probits/Log(Dose))
GA Very Severe	Lethal	70	12
GA Severe	Severe	50	12
GA Moderate	Moderate	1.2	12
GA Mild	Mild	0.4	4.5

[a] The median toxicity is an estimate for a 2-minute exposure.

Median Toxicities and Probit Slopes for Inhaled GD

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	PS (Probits/Log(Dose))
GD Very Severe	Lethal	33	12
GD Severe	Severe	25	12
GD Moderate	Moderate	0.6	12
GD Mild	Mild	0.2	4.5

[a] The median toxicity is an estimate for a 2-minute exposure.

Median Toxicities and Probit Slopes for Inhaled GF

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	Probit Slope (Probits/Log(Dose))
GF Very Severe	Lethal	41	12
GF Severe	Severe	31	12
GF Moderate	Moderate	1.2	12
GF Mild	Mild	0.4	4.5

[a] median toxicity is an estimate for a 2-minute exposure.

Inhaled GA, GD, or GF Injury Profiles

Time Point (Min)	GA, GD or GF Mild	GA, GD or GF Moderate	GA, GD or GF Severe	GA, GD or GF Very Severe
1	0	2	3	4
3	1	2	3	4
15	1	2	3	4[a]
150	0	2	3	
1000	0	2	2	
1940	0	1	2	
8640	0	1	1	

[a] Death is modeled to occur at this point.

GA, GD, GF MTOR

Injury Profile	DOW	CONV	RTD
GA, GD or GF Mild	0%	Day 2: 100%	Day 8: 100%
GA, GD or GF Moderate	0%	Day 3: 100%	Day 15: 100%
GA, GD or GF Severe	0%	Day 5: 33.3% Day 6: 33.3% Day 7: 33.4%	Day 31: 100%
If casualties receive self-aid/buddy aid without further medical treatment:			
GA, GD,[a] or GF Very Severe, $X^{eff}_{GA,GD,GF,ih}$[b] < 3×LCt_{50}	0%	Day 15: 100%	0%
GB, GD,[a] or GF Very Severe, $X^{eff}_{GA,GD,GF,ih}$[b] ≥ 3×LCt_{50}	Day 2: 100%	0%	0%
If casualties receive self-aid/buddy aid and further medical treatment:			
GB, GD,[a] or GF Very Severe, $X^{eff}_{GA,GD,GF,ih}$[b] < 5×LCt_{50}	0%	Day 15: 100%	0%
GB, GD,[a] or GF Very Severe, $X^{eff}_{GA,GD,GF,ih}$[b] ≥ 5×LCt_{50}	Day 2: 100%	0%	0%

[a] The Very Severe models in this table will only apply for GD if pyridostigmine bromide (PB) treatment is also used; otherwise, any casualty in the Very Severe cohort will be modeled as killed in action (KIA).

[b] $X^{eff}_{GA,GD,GF,ih}$ is the Effective CBRN Challenge of inhaled GA, GD, or GF.

Lewisite (L)

L human toxicity data are essentially nonexistent, and older reports estimate the L human toxicity parameters from old experimental animal studies. Many papers cite the 1946 Gates et al.[1] report summarizing the animal data used to derive the human toxicity parameters. It offers references to the animal studies performed in the 1940s or earlier; however, obtaining these studies to verify the data was not possible. The only collective toxicity values for L is published in the 2005 Department of Defense (DOD) publication, FM 3-11.9,[2] which provides the estimated toxicity parameters for L based on the toxicity recommendations for sulfur mustard (HD). Although, L is a vesicant similar to HD, it has a completely different mechanism of toxicity. Another significant difference is that HD causes delayed injuries, while L results in rapid toxic effects. Due to the differences between HD and L and no evidence to support that HD toxicity values can be used for L, the IDA team deemed it not appropriate to use the estimated toxicity parameters published in FM 3-11.9 as the parameters for L in this paper. The IDA team recommends further research to determine whether the proposed HD toxicity parameters can be used for L or new research to estimate toxicity values for L.

Since the median toxicities and PSs for L cannot be estimated, the L Injury Profiles and L MTOR table also cannot be derived. The L chapter focuses on summarizing the available information in the literature on the physiological effects, injury profiles and effects of medical treatment for L and compares their similarities and differences to HD.

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[1] Marshall Gates, Jonathan W. Williams, John A. Zapp, "Arsenicals," in *Chemical Warfare Agents, and Related Chemical Problems Part I-II*, vol. 1 of Summary Technical Report of Division 9, NRDS, ed. the Joint Research and Development Board Programs Division (Washington, DC: Office of Scientific Research and Development, 1946), declassified by DOD Memo 8/2/60, AD234270.

[2] U.S. Army Chemical School (USACMLS), *Potential Military Chemical/Biological Agents and Compounds*, FM 3-11.9/MCRP 3-37.1B/NTRP 3–11.32/AFTTP(I) 3-2.55 (Washington, DC: U.S. Government Printing Office, January 2005).

Contents

Appendices

1. Introduction

Since 1994, the Institute for Defense Analyses (IDA) has supported the U.S. Army Office of the Surgeon General (OTSG) in the Medical Chemical, Biological, Radiological, and Nuclear (CBRN) Defense Planning and Response Project in its planning, preparation, and exercises to defend against CBRN weapons use against U.S. military personnel. The objective of the project is to ensure that the U.S. military medical community can successfully fulfill its mission in a CBRN environment.

Over the past several years, OTSG has been responsible for generating a North Atlantic Treaty Organization (NATO) standard for estimating the casualties that would result from the use of CBRN weapons in battlefield attacks against Allied forces. To support this effort, IDA had adapted earlier existing symptom-based methodologies[3] for estimating the number, type, and timing of CBRN casualties. NATO promulgated the methodology as NATO Standardization Agreement (STANAG) 2553, *Allied Medical Publication 8 (AMedP-8(C)): NATO Planning Guide for the Estimation of CBRN Casualties*.[4] In continued support to OTSG, IDA is currently developing the next edition of the NATO CBRN casualty estimation methodology, which is titled Allied Medical Publication 7.5 (*AMedP-7.5*).[5]

The NATO CBRN Medical Working Group specifically restricted the *AMedP-8(C)* model from including the estimated effects of medical treatment because a standardized model for medical treatment has not been developed. Following to the promulgation of *AMedP-8(C)*, OTSG has requested a study that addresses the impact of medical treatment

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[3] George H. Anno et al., "Symptomatology of Acute Radiation Effects in Humans after Exposure to Doses of 0.5-30 Gy," *Health Physics* 56, no. 6 (June 1989): 821–838; Sheldon G. Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, DNA-TR-92-134 (Alexandria, VA: Defense Nuclear Agency, 1993); Arthur P. Deverill and D. F. Metz, *Defense Nuclear Agency Improved Casualty Estimation (DICE) Chemical Insult Program Acute Chemical Agent Exposure Effects*, DNA-TR-93-162 (Alexandria, VA: Defense Nuclear Agency, May 1994); George H. Anno et al., *Biological Agent Exposure and Casualty Estimation: AMedP-8 (Biological) Methods Report* (Arlington, VA: General Dynamics Advanced Information Systems, May 2005); Gene E. McClellan, George H. Anno, and Leigh N. Matheson, *Consequence Analytic Tools for NBC Operations*, vol.3 of *Chemical Agent Exposure and Casualty Estimation* (Alexandria, VA: Defense Special Weapons Agency, 1998); George H. Anno et al., *Consequence Analytic Tools for NBC Operations*, vol. 1 of *Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever*, DSWA-TR-97-61-V1 (Alexandria, VA: Defense Special Weapons Agency, 1998).

[4] North Atlantic Treaty Organization (NATO), *AMedP-8(C): NATO Planning Guide for the Estimation of CBRN Casualties*, STANAG 2553 (Brussels, Belgium: NATO, March 2011).

[5] NATO changed its document numbering scheme; therefore, *AMedP-8(C)* is now *AMedP-7.5*.

on *AMedP-8(C)* casualty estimation methodology. In response, IDA developed the *AMedP-8(C)* patient estimation methodology and specific parameters for a number of agents and effects.[6] From 2010 to 2014, at the request of OTSG, IDA also developed the "untreated" models and "treated" models of CBRN casualty estimation for five additional chemical agents and 10 additional biological agents.[7]

More recently, OTSG has requested that IDA develop untreated and treated models of CBRN casualty estimation for five additional chemical agents. The chemical warfare agents of interest to OTSG are ammonia (NH_3), tabun (GA), soman (GD), cyclosarin (GF), and lewisite (L). Because the models will be included in *AMedP-7.5*, which is an unclassified publication, we did not use classified references in the analyses. This paper proposes the untreated and treated models for the five additional chemical agents.

The goal of this effort was two-fold: (1) document the derivation of the untreated and treated parameter values for modeling human response to the five additional chemical agents, and (2) present the tables, figures, and other content needed to incorporate the new human response models into *AMedP-7.5* and its technical reference manual.

A. Overview of the *AMedP-7.5* Casualty Estimation Methodology

This section[8] provides an overview of the casualty estimation methodology to give the readers an understanding of how the proposed models presented in this paper will be integrated. The subsequent chapters of this paper will present the derivation of the agent-specific models and parameter values for untreated and treated cases. Each chapter begins with a derivation of the untreated model and concludes with a section on the treated model, highlighting the effects of medical treatment.

1. Definitions

These definitions are consistent with those used in Study Draft 3 of *AMedP-7.5*, many of which come from the NATO Terminology Management System (NTMS).

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[6] Carl A. Curling et al., *The Impact of Medical Care on Casualty Estimates from Battlefield Exposure to Chemical, Biological and Radiological Agents and Nuclear Weapon Effects*, IDA Document D-4465 (Alexandria, VA: Institute for Defense Analyses, March 2012).

[7] Carl A. Curling et al., *Parameters for the Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia*, IDA Document D-4132 (Alexandria, VA: Institute for Defense Analyses, November 2010); Oxford et al., *Parameters for Estimation of Casualties from Phosgene, Chlorine, Hydrogen Chloride, Cyanide, Hydrogen Sulfide, B. pseudomallei, Eastern and Western Equine Encephalitis Viruses, Ricin, and T-2 Mycotoxin*, IDA Paper P-5140 (Alexandria, VA: Institute for Defense Analyses, September 2015).

[8] This section has some overlap with Oxford et al., *Parameters for Estimation of Casualties from Phosgene, Chlorine, Hydrogen Chloride, Cyanide, Hydrogen Sulfide*.

- An **icon** is a group of individuals that share a common location over time.
- **CBRN Challenge** is the time-varying cumulative amount or degree of CBRN agent or effect estimated to be present in the physical environment with which the icons are interacting. For chemical agents with concentration-based effects, this definition also includes the time-dependent gas concentration estimated to be present in the physical environment with which icons are interacting.
- **Effective CBRN Challenge** is the cumulative amount or degree of CBRN agent or effect that is estimated to actually affect an icon, after accounting for factors such as breathing rate and protective equipment. *Note:* Effective CBRN Challenge is an umbrella term used in *AMedP-7.5*. In the context of the present paper, the terms *dose*, *concentration time* (Ct), or *peak concentration* may be used instead of Effective CBRN Challenge.
- **Injury Severity Level** is defined in Table 1. The Injury Severity Levels for chemical, radiological, and nuclear agents and effects are described solely in terms of observable symptoms.
- **Wounded in action (WIA)** is the casualty category assigned to "a battle casualty other than "killed in action" who has incurred an injury due to an external agent or cause as a result of hostile action.[9]
- **Casualty criterion** is the user-specified Injury Severity Level used to determine whether an individual is WIA (see Figure 1). The syntax and more specific definition for each of the possible choices for the casualty criterion are as follows:[10]
  - WIA(1^+): an individual manifesting signs and/or symptoms of Injury Severity Level 1 or greater is considered WIA.
  - WIA(2^+): an individual manifesting signs and/or symptoms of Injury Severity Level 2 or greater is considered WIA.
  - WIA(3^+): an individual manifesting signs and/or symptoms of Injury Severity Level 3 or greater is considered WIA.

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[9] North Atlantic Treaty Organization (NATO), *AMedP-13(A): NATO Glossary of Medical Terms and Definitions*, STANAG 2409 (Brussels, Belgium: NATO, 6 May 2011), 2-65. Note that this definition differs from the NTMS, which states that a WIA "has incurred a non-fatal injury," thereby precluding the possibility that a WIA can later die—an incorrect definition.

[10] Note that since "Severe" symptoms are defined as those that preclude an individual's ability to conduct the assigned mission, a casualty criterion of WIA(4+) is not allowed.

Table 1. *AMedP-8(C)* Injury Severity Level Definitions

Severity Level	Degree	Description
0	No Observable Injury	Although some exposure to an agent or effect may have occurred, no observable injury (as would be indicated by manifested symptoms) has developed. Alternately, recovery from a prior injury is complete.
1	Mild	Injury manifesting symptoms (and signs for biological agents) of such severity that individuals can care for themselves or be helped by untrained personnel. Condition may not impact ability to conduct the assigned mission.
2	Moderate	Injury manifesting symptoms (and signs for biological agents) of such severity that medical care may be required. General condition permits treatment as outpatient and some continuing care and relief of pain may be required before definitive care is given. Condition may be expected to interrupt or preclude ability to conduct the assigned mission.
3	Severe	Injury manifesting symptoms (and signs for biological agents) of such severity that there is cause for immediate concern, but there is no imminent danger to life. Individual is acutely ill and likely requires hospital care. Indicators are questionable—condition may or may not reverse without medical intervention. Individual is unable to conduct the assigned mission due to severity of injury.
4	Very Severe	Injury manifesting symptoms (and signs for biological agents) of such severity that life is imminently endangered. Indicators are unfavorable—condition may or may not reverse even with medical intervention. Prognosis is death without medical intervention. Individual is unable to conduct the assigned mission and is not expected to return to the mission due to severity of injury.

Source: Carl A. Curling et al., Technical Reference Manual: Allied Medical Publication 8(C), NATO Planning Guide for the Estimation of Chemical, Biological, Radiological. And Nuclear (CBRN) Casualties, IDA Document D-4082 (Alexandria, VA: Institute for Defense Analyses, August 2010), 14.

Note for Table 1: Some minor modifications have been made to ensure consistency with Study Draft 3 of AMedP-.7.5

- **Killed in action (KIA)** is the casualty category assigned to "a battle casualty who was killed outright or who died before reaching a medical treatment facility."[11] Consistent with Study Draft 3 of *AMedP-7.5*, a KIA was previously WIA, but since KIAs occur on the same day as the injury, they are only *reported* as KIA.

[11] NTMS, NATO Agreed 2011-11-07.

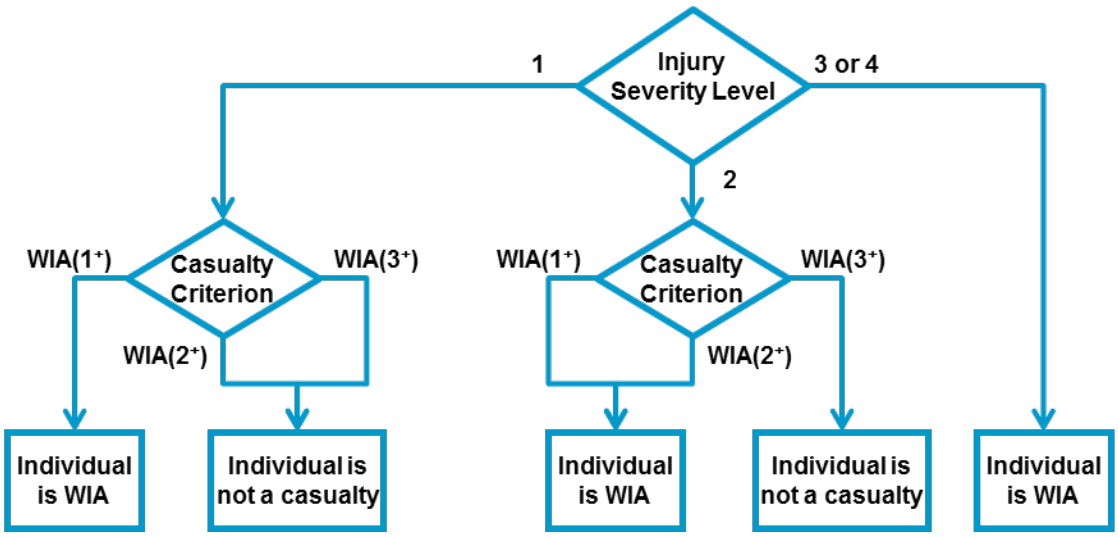

Figure 1. Relationship of Casualty Criterion, Severity Level, and WIA

- **Died of wounds (DOW)** is the casualty category assigned to "a battle casualty who died after having entered the medical care system."[12] Consistent with Study Draft 3 of *AMedP-7.5* and the definition of KIA, "the medical care system" is taken to mean a Role 1 or higher Medical Treatment Facility (MTF). If a casualty dies during medical evacuation, he or she is considered KIA. Further, a DOW was previously WIA.
- **Convalescent (CONV)** is the casualty category assigned to a patient who is "mostly ambulatory [and] requires limited therapeutic intervention and administration of oral medications performed by the patient."[13] Consistent with Study Draft 3 of *AMedP-7.5*, CONV refers to outpatient medical care. A CONV was previously WIA. Casualties whose recovery time can be estimated will Return to Duty (RTD), and those with an unknown period of recovery or permanent disability will remain in CONV.
- **Return to duty (RTD)** is the casualty category assigned to a patient who has undergone "the administrative process of releasing a patient from medical treatment facility to his or her unit."[14] Consistent with Study Draft 3 of *AMedP-7.5*, an RTD was previously WIA (and possibly CONV) but has recovered. Further, *AMedP-7.5* does not consider the impact of theater evacuation policy on RTD. Individuals in the RTD category are simply *available* to return to their duties.

[12] NTMS, NATO Agreed 2011-11-07.

[13] North Atlantic Treaty Organization (NATO), *AMedP-13(A)*, 2-15.

[14] NTMS, NATO Agreed 2014-06-25.

- **Medical countermeasures** are "those medical interventions designed to diminish the susceptibility of personnel to the lethal and damaging effects of chemical, biological, and radiological hazards and to treat any injuries arising from challenge by such hazards."[15] Under the umbrella of medical countermeasures are prophylaxis and medical treatment.
  - **Prophylaxis** is medical countermeasures administered before the onset of signs and symptoms (S/S).
  - **Medical treatment** is the medical countermeasures administered after the onset of S/S.
- **Self-aid** is "[l]imited care provided by a patient for oneself, such as the self-administration of oral medication."[16] It may be prophylaxis or medical treatment.
- **Buddy aid** is the "initial aid provided by a non-medically-trained service member to a sick, injured or wounded comrade (buddy)."[17] It may be prophylaxis or medical treatment.
- **Protection factor (PF)** is a "measure of the effectiveness of a protective device or technique in preventing or reducing exposure to chemical, biological, radiological, and nuclear substances, or of a medical treatment in preventing or reducing the physiological effects of such substances."[18] Consistent with Study Draft 3 of *AMedP-7.5*, a PF is the factor by which the CBRN Challenge is reduced (e.g., a mask protection factor of 10 reduces an inhaled *Bacillus anthracis* dose from 100 spores to 10 spores).
- **Injury Profile** is a tabular description of the progression of injury expressed in terms of the step-wise Injury Severity Level changes over time, with time "zero" defined as the time at which the Effective CBRN Challenge stops accumulating. Injury Profiles only show time points at which the Injury Severity Level changes. In some cases, the last entry in an Injury Profile is non-zero, in which case the time to full recovery is undefined. The intent is that the different Injury Profiles for a given agent represent sets of symptoms that can be clinically differentiated.

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[15] NTMS, Not NATO Agreed 2006-07-01.

[16] North Atlantic Treaty Organization (NATO), *AMedP-13(A)*, 2-57.

[17] Ibid., 2-9.

[18] NTMS, NATO Agreed 2014-04-10.

2. Summary of *AMedP-7.5* Casualty Estimation Methodology[19]

Casualty estimation in *AMedP-7.5* begins with an externally provided quantitative estimate of the CBRN Challenge for each icon. The number of personnel per icon is required. Other information that will affect the casualty estimate, but is optional, includes things like breathing rate, vehicle or shelter occupied, and any individual protective equipment used.

Given the previous information, the methodology calculates the Effective CBRN Challenge for each icon, which is given as input to the human response model for the specific agent of interest. The methodology, which is based on the outputs of the human response model, the values of a few user-defined methodology parameters, and the definitions of the different casualty categories, generates a casualty estimate. The output is reported with 1-day time resolution.

The user-defined methodology parameters are important for the present paper. The following two parameters have some impact on the casualty category assignment process shown in Figure 2:

- The first parameter is the time at Injury Severity Level 4 sufficient to cause death from untreated chemical, nuclear blast, or nuclear burn injuries ($T_{death\text{-}CN\text{-}SL4}$). Untreated[20] casualties with a chemical, nuclear blast, or nuclear burn injury who spend this threshold amount of time at Injury Severity Level 4 are assumed to die. The default value is 15 minutes, but the user can specify any desired value. This parameter affects the answer to the question, "Will the casualty die?," in Figure 2.
- The second parameter is the time required for an individual who is WIA to reach a MTF (T_{MTF}). Given the definitions of KIA and DOW, T_{MTF} determines whether a WIA who dies is KIA or DOW (see Figure 2). The default value is 30 minutes, and a user can specify any value up to (but excluding) 1 day. The methodology is built around the assumption that casualties reach an MTF *within* 1 day of becoming WIA.

Figure 2 represents part of the logic used by the methodology to "translate" from human response model outputs to a casualty estimate. Medical treatment, when available, has a significant impact on the human response itself and the translation from human response to casualty estimate—hence, the focus on separate untreated and treated models.

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[19] The discussion here applies to chemical agents. Some portions of the methodology are different for radiological and/or nuclear challenges, but these differences are not explained here.

[20] Or *not yet treated* casualties en route to a MTF.

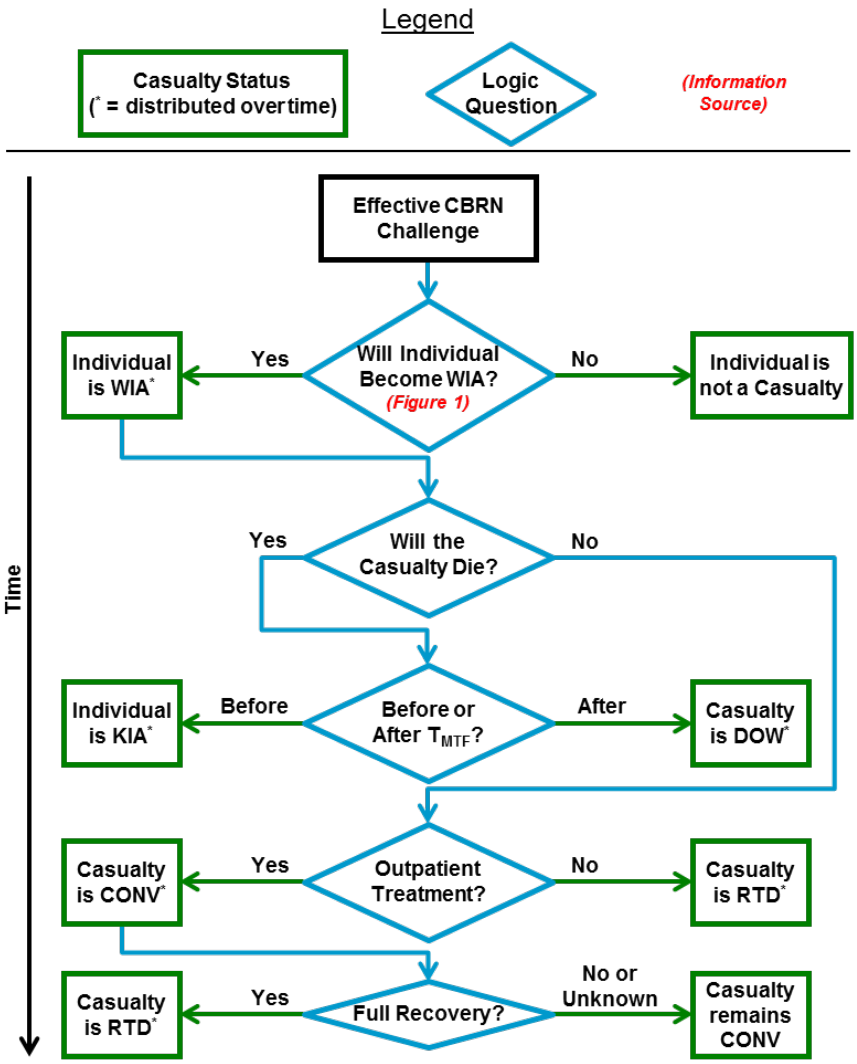

Figure 2. Decision Tree for Assignment of Casualty Category

For chemical agents, the Effective CBRN Challenge is used in a series of probabilistic calculations (using median toxicities and associated probit slopes (PSs) to determine the number of individuals that will exhibit different levels of effect (labeled mild, moderate, severe, or lethal). Each level of effect corresponds to an Injury Profile.[21] In contrast to *AMedP-8(C)*, *AMedP-7.5*'s use of probabilistic estimation of the number of personnel associated with each Injury Profile means that the expected natural variation in a

[21] This approach differs from *AMedP-8(C)*, which correlated Injury Profiles with dosage bands and binned into that band anyone whose dosage was in a certain range. A recent IDA analysis has shown that the error introduced by the dosage-binning method can be inordinately large, so *AMedP-7.5* has been modified to use probabilistic calculations of the number injured at different severities. See Lucas A. LaViolet and Aaron D. Danilack, *2014 Review on the Extension of the AMedP-8(C) Methodology to New Agents, Materials, and Conditions*, IDA Document D-5226 (Alexandria, VA: Institute for Defense Analyses, August 2015).

population is estimated but that the response of a particular individual cannot be estimated. If medical treatment is not considered (untreated), the Injury Profile dictates casualty outcomes, and every casualty following that Injury Profile has the same outcome. In contrast to *AMedP-8(C)*, *AMedP-7.5* will use the rule that if the Injury Profile returns to Injury Severity Level 0, untreated casualties are estimated to RTD. CONV is never used for untreated casualties since the definition of CONV is related to outpatient *treatment*. If medical treatment is considered (treated), the Injury Profile is followed until casualties reach the MTF, at which point the outcomes are dictated by a medical treatment outcome reporting (MTOR) table, which accounts for the effects of medical treatment and might probabilistically split among several different outcomes the casualties who were following a certain Injury Profile. All casualty categories defined in Subsection 1.A.1 are used in treated models.

B. Research Approach

1. Assumptions and Limitations

a. Administrative declaration of casualties

We recognize that in cases of known or suspected CBRN exposure, a commander may decide to withdraw soldiers and have them monitored at an MTF, even if none or few have definite symptoms, or may decide to hold them for monitoring at the MTF after their symptoms have disappeared. Particularly since the effects of some agents/effects may be delayed for hours before the onset of GB life-threatening symptoms and the agent identity might be unknown in a real-world situation, this course of action is prudent. However, since the methodology is *symptom based*, it does not account for administrative decisions to declare a person an "asymptomatic casualty" or to delay RTD.

b. Secondary and/or higher effects

As stated in *AMedP-8(C)*, "[h]uman response is modeled solely as a function of primary and direct physiological effects. Battle stress cases and indirect effects (e.g., injuries resulting from car accidents following an attack, burns due to secondary fires, or opportunistic infections) are not considered."[22]

2. Hierarchy of Source Data

The usefulness of the toxicity values presented in the subsequent chapters of this paper depends heavily on the availability of pertinent data sources and the quality of data

[22] North Atlantic Treaty Organization (NATO), *AMedP-8(C)*, 1-2.

found therein. When raw data were available, these data were used directly to define original toxicity values or independently verify values calculated elsewhere. When data were limited, we identified issues and gaps and developed a strategy to generate the best possible model input parameter values given the constraints. This subsection outlines the methodological approach chosen to manage the varying levels of data availability and quality and ultimately ranks each source type according to its likelihood to lead to useful model parameters.

The literature review for each agent included a wide range of sources. Although controlled human experiments conducted specifically to better understand the human response to exposure are ideal, little such data were available for the agents considered in this paper. Such data would be ideal because the exact parameters required for modeling human response—including inhaled dose and the resulting effects—are often captured, allowing for dose-dependent human response models.

It is also rare to encounter a record of accidental exposure for which the dose of agent inhaled is precisely known. For a few agents, data exist from accidental exposures for which the exposed dose is unknown. Nonetheless, these accounts sometimes provide useful descriptions of the injury and its progression and can inform parts of the model.

In the absence of useful human data, controlled animal studies are typically the best sources for deriving model parameters. Primate species, due to their genetic similarity to humans, are generally viewed as the best models for human response effects, followed by non-primate mammals and finally non-mammalian species. Yet, even documented animal experimental results are sometimes difficult to find or may not supply the needed information. In this case, parameters can be derived from expert opinion or extrapolation from similar agents. As a last resort, parameters can simply be estimated. Table 2 provides a summary list of the various types of data sources considered, ordered by the expected relevance of the source data to developing model parameters.

3. Explicit Documentation

Chapters 3–5 are designed to allow the modelers who are implementing the models described here to critique our assumptions and supplement data gaps with better or newly generated information as it becomes available. Each chapter explicitly documents all decisions and identifies knowledge gaps to aid in future modeling efforts and highlight weaknesses in this model. While we believe the parameters selected in this document represent the best possible values for the human response models at this time, their applicability may need to be reassessed as assumptions change and particularly as new data become available in the future.

Table 2. Literature Review Data Source Preferences

Data Source	Relevance of Data
Controlled human experiments	Highest
Accidental or intentional exposures	
Controlled animal studies	
Primates	
Non-primate mammals	
Non-mammals	
Extrapolation from similar agents	
Expert opinion	
Best guesses	Lowest

2. Overview of Chemical Agent Models

A. Introduction

The model parameters for the five chemical agents will be described in this paper. These five chemical agents comprise of one toxic industrial compound (TIC), three nerve agents and a blister agent. NH_3 is referred to as a TIC because of its use in industry. GA, GD, and GF are nerve agents that affect the nervous system and disrupt bodily functions which are vital to an individual's survival. L is blister agent that acts as a vesicant and lung irritant.

This chapter identifies and briefly describes documents that were used as methodological or technical references for the agents, provides some context for understanding how the chemical agent models work, and briefly discusses some assumptions and limitations of the analysis. Chapters 3 through 5 describe the model development and recommended parameter values for the five chemical agents.

B. Foundational Documents

This section has some overlap with IDA document D-5140.[23]

We used three IDA publications as methodological guides in the derivation of the chemical agent models. While these documents are not frequently cited in the following chapters, we consulted them frequently for guidance.

1. *Technical Reference Manual: NATO Planning Guide for the Estimation of Chemical, Biological, Radiological, and Nuclear (CBRN) Casualties, Allied Medical Publication-8(C)*

This document[24] "detail[s] the derivations of the human response methodologies" for sarin (GB), VX, and sulfur mustard (HD). In essence, it is a summary of the work conducted to develop the chemical agent models included in *AMedP-8(C)*.

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[23] Oxford et al., *Parameters for Estimation of Casualties from Phosgene, Chlorine, Hydrogen Chloride, Cyanide, Hydrogen Sulfide*.

[24] Curling et al., *Technical Reference Manual*, 9.

2. *The Impact of Medical Care on Casualty Estimates from Battlefield Exposure to Chemical, Biological and Radiological Agents and Nuclear Weapon Effects*

This document[25] is the first IDA publication that describes the treated models. In addition to defining the framework of the model, it also documents the derivation of the treated models for GB, VX, and HD (and other agents/effects).

3. Parameters for Estimation of Casualties from Phosgene, Chlorine, Hydrogen Chloride, Cyanide, Hydrogen Sulfide, B. pseudomallei, Eastern and Western Equine Encephalitis Viruses, Ricin, and T-2 Mycotoxin

This document[26] describes the literature searches, analytical decisions, and recommended parameter values for modeling human response to five chemical warfare agents and five biological warfare agents for treated and untreated cases. The chemical warfare agents are phosgene (CG), chlorine (Cl_2), hydrogen cyanide (AC), cyanogen chloride (CK) and hydrogen sulfide (H_2S), and the five biological warfare agents are *Burkholderia pseudomallei* (the causative agent of melioidosis), Eastern equine encephalitis (EEE) virus, Western equine encephalitis (WEE) virus, ricin, and T-2 mycotoxin. The recommended untreated and treated parameter values in this document will be included in *AMedP-7.5*.

C. Important Technical References

At the outset of the search for data to inform the model development, we identified a few particularly relevant and useful references. This section briefly describes these references and explains their role in the development of the untreated and treated models for the five chemical agents. Together, these documents provided a useful overview of the human response to each agent and served as a starting point for gathering the relevant underlying data. We also used a number of other sources for each agent, as cited in the chapters below.

This section has some overlap with IDA document D-5140.[27]

1. Field Manual (FM) 3-11.9

Department of Defense (DOD) publication FM 3-11.9[28] provides estimated toxicity parameters for a wide variety of chemical agents. Its nerve and mustard agent parameter

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[25] Curling et al., *The Impact of Medical Care*.

[26] Oxford et al., *Parameters for Estimation of Casualties from Phosgene, Chlorine, Hydrogen Chloride, Cyanide, Hydrogen Sulfide*.

[27] Ibid.

value estimates are based on human or animal data from the Reutter-Wade report,[29] the Grotte-Yang report,[30] or the early results of the Low-Level Chemical Warfare Toxicology Research Program (LLTP).[31] The Reutter-Wade report contains "an extensive review of the relevant human and animal toxicological data, and a compilation of the more often-quoted existing human toxicity estimates, along with data, assumptions, and rationale upon which those estimates were based (when available)."[32] It is the first large-scale effort to develop generally accepted parameter value estimates for chemical agents. The Grotte-Yang report provides a summary of the recommendations from a subject matter expert (SME) review of the Reutter-Wade report. In some cases, it recommends values that differ from the Reutter-Wade report. It concludes by stating that "these values are the best estimates we have for these six agents, and they represent the consensus of representatives of the scientific, medical, analytical and operational communities based on extensive examination of available data and careful review of that examination."[33]

2. The LLTP

The LLTP began in 1998 and was designed to fill in data gaps for GB, GD, GF, and VX in response to the Reutter-Wade report. The particular focus was the future development of revised defense-minded toxicity estimates. The LLTP produced new data from studies in which animals were acutely exposed to a single vapor dose of an agent of interest. Analysts used the new data to develop new toxicity estimates. Although these publications are annual reports, the study team chose to use the final report as the source of toxicity estimates for the LLTP.[34] As the report states, "[t]he results are scientifically auditable, transparent and focused on the military operator as the population of con-

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[28] U.S. Army Chemical School (USACMLS), *Potential Military Chemical/Biological Agents and Compounds*, FM 3-11.9/MCRP 3-37.1B/NTRP 3–11.32/AFTTP(I) 3-2.55 (Washington, DC: U.S. Government Printing Office, January 2005).

[29] Sharon A. Reutter and John V. Wade, *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier* (U), ERDEC-SP-018 (Aberdeen Proving Ground, MD: Edgewood Research Development and Engineering Center, 1994), SECRET.

[30] Jeffrey H. Grotte and Lynn I. Yang, *Report on the Workshop on Chemical Agent Toxicity for Acute Effects*, IDA Document D-2176 (Alexandria, VA: Institute for Defense Analyses, June 2001).

[31] S. A. Thomson et al., *Low Level Chemical Warfare Agent Toxicology Research Program FY02-FY07 Report and Analysis*, AFRL-RH-WP-TR-2008-0093 (Wright Patterson AFB, OH: Air Force Research Laboratory, Human Effectiveness Directorate, Bioscience and Protection Division Counter-Proliferation Branch, June 2008).

[32] Reutter and Wade, *Review of Existing Toxicity Data*, Abstract.

[33] Grotte and Yang, *Report on the Workshop on Chemical Agent Toxicity*, 11.

[34] Thomson et al., *Low Level Chemical Warfare Agent Toxicology Research Program*.

cern."[35] In the judgment of the IDA team, the parameter value estimates published in the LLTP supersede all prior estimates where there is a difference since the LLTP provides the most current parameter values.

3. The Department of Homeland Security Chemical Security Analysis Center (CSAC) Report

CSAC published a series of reports between 2009 and 2011 on its estimates of median toxicities, PSs, and toxic load exponents for military-relevant human exposure to several TICs, one of which was NH_3.[36] We refer to these reports as the CSAC reports.

Each report contains a database of median toxicities and PSs derived by CSAC from individual data sets from historical animal experiments. Full citations and experiment summaries are provided for each of the original data sets used in the CSAC analyses, and many of the references can be easily obtained (although some are restricted access). The only limitation on the literature base was that no classified references were used. CSAC used average species masses and respiratory minute-volumes reported by Bide, Armour and Yee[37] to extrapolate the mammalian median toxicities to humans using an average human body mass of 70 kg and a minute-volume of 15 L/min.[38] For PSs, CSAC used a weighted geometric mean of the individual PSs in its database to estimate a PS for the healthy human subpopulation. CSAC assumed that PSs from laboratory animals are a reasonable estimate of the PS of the healthy human subpopulation, as opposed to the general human population in which the variance is likely larger (lower PSs). The healthy human subpopulation is the more accurate representation of the military population of interest for *AMedP-7.5*.

One distinguishing feature of CSAC's work was that unlike many previous estimates of human toxicity parameters, CSAC did not make assumptions about the sensitivity of humans relative to other mammals. It compared its results to previous human toxicity estimates and, where it disagreed, explained why its estimate should be used instead of the previous estimate.

Since FM 3-11.9 has either no estimate or outdated estimates for NH_3, we chose to use CSAC estimates, where available, as the best estimates. We used the median toxicity

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[35] Ibid., 3.

[36] D. R. Sommerville et al., *Review and Assessment of Ammonia Mammalian Lethality Data and the Development of a Human Estimate*, CBRNIAC-SS3-829-1 (Aberdeen Proving Ground, MD: Chemical Security Analysis Center, Department of Homeland Security, 2011).

[37] R. W. Bide, S. J. Armour, and E. Yee, "Allometric Respiration/Body Mass Data for Animals to be Used for Estimates of Inhalation Toxicity to Young Adult Humans," *Journal of Applied Toxicology* 20, no. 4 (July–August 2000): 273–290.

[38] This is also the standard breathing rate used in *AMedP-8(C)*. It is associated with light exertion.

estimates for 2-minute exposures, consistent with the method used to develop the untreated models for GB, VX, and HD.[39]

4. Edgewood Chemical Biological Center (ECBC) Technical Report (TR) 856

ECBC-TR-856[40] describes recent ECBC work to derive human toxicity estimates for the military subpopulation for 17 TICs, including one of the chemicals of interest in this current paper. ECBC-TR-856 and the NH_3 CSAC report give similar estimates, which is not surprising since the supporting analyses were apparently conducted simultaneously by the same analysts, including the same lead author. The few differences between ECBC-TR-856 and the CSAC report stem from the fact that ECBC-TR-856 had a more limited literature base than the CSAC report.[41] Given the smaller literature base for ECBC-TR-856, we chose to use CSAC estimates when CSAC reports and ECBC-TR-856 reported different estimates.

5. Documents Related to Various Exposure Guidelines

Over the years, a number of different public exposure guidelines have been published for various chemical compounds. The primary three types of guidelines relevant for the present analysis are Temporary Emergency Exposure Limits (TEELs), Emergency Response Planning Guidelines (ERPGs), and Atmospheric Exposure Guideline Levels (AEGLs). Immediately Dangerous to Life and Health (IDLH) values are also of interest, but their derivation is generally less well documented.

The utility of the various guidelines is that the documentation supporting their derivation is useful as a source of original data that could be used to develop mild and moderate median effective dosage (concentration time) (ECt_{50}) estimates. As warranted, the documents consulted are cited in Chapters 3–5. However, our preference is to not compare the various guidelines to the median toxicity estimates presented later in this paper, because we view the guidelines as overly conservative estimates for the military population, which is typically considered a "healthy subpopulation" of the general population. Indeed, guidance on the creation of AEGLs directs that if human data are not available and data on the species that "best" represents humans are also not available, data from the

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[39] Curling et al., *Technical Reference Manual*, 64–72, 102–110.

[40] Douglas R Sommerville, Stephen R. Channel, and John J. Bray, *Proposed Provisional Human Toxicity Estimates for Several Toxic Industrial Chemicals*, ECBC-TR-856 (Aberdeen Proving Ground, MD: U.S. Army Research, Development and Engineering Command, Edgewood Chemical Biological Center, November 2012).

[41] Page 10 of ECBC-TR-856 states that the authors relied on the National Research Council (NRC) Acute Exposure Guideline Levels (AEGLs) Committee to "vet" the literature and built upon that foundation. They also used other sources in some cases, but it seems that they did not conduct a complete literature survey.

most sensitive species should be used.[42] An uncertainty factor of up to 10 can also be applied to lower the estimates even further. The specific value of the uncertainty factor is based on a subjective assessment of the quality of the available data. This approach makes sense for protecting the general population, but it also renders the resulting thresholds inappropriate for comparison with military toxicity estimates. Even if the military toxicity estimates were compared with civilian guidelines, one should expect significant differences, such that there seems to be little value in performing such comparisons.

One further point to make here, rather than in each chemical agent chapter, is that for each agent, the various guideline documents make reference to a number of known instances of long-term occupational exposures. Such data cannot be used for deriving ECt_{50} estimates because there are too many uncontrolled or unknown factors. Data for this paper must relate to a *single* exposure for some known (or estimable) concentration-time profile.

6. Medical Aspects of Chemical Warfare

This volume[43] in the Textbooks of Military Medicine series contains three chapters on nerve agents, one chapter on vesicants, and one chapter on TICs in general. The chapters provide information on clinical manifestations of exposure, treatment, and antidote options, recovery, and general information on the use of these agents as chemical weapons. Our main use of the chapters was to identify sources of original data and to use the chapters as a source of qualitative confirmation to show that the derived parameters are consistent with prior knowledge, but we also occasionally used them directly to inform the parameterization.

7. Medical/Field Management of Chemical Casualties Handbooks

These two publications[44] from the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) provide general overviews of the clinical manifestation of exposure, treatment, antidote options, recovery, and general information on the use of the G-series nerve agents, L, and NH_3 as chemical weapons. Our main use of these sources was as qualitative confirmation that the derived parameters are consistent with prior knowledge, but we also occasionally used them directly to inform the parameterization.

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[42] National Research Council, *Acute Exposure Guideline Levels for Selected Airborne Chemicals*, vol. 3 (Washington, DC: The National Academies Press, 2003), 4.

[43] Shirley D. Tuorinsky, ed., *Medical Aspects of Chemical Warfare*, Textbooks of Military Medicine (Washington, DC: Office of the Surgeon General, Department of the Army, 2008).

[44] Gary Hurst et al., eds., *Medical Management of Chemical Casualties Handbook*, 4th ed. (Aberdeen Proving Ground, MD: USAMRICD, Chemical Casualty Care Division, February 2007); Gary Hurst et al., eds., *Field Management of Chemical Casualties Handbook*, 3rd ed. (Aberdeen Proving Ground, MD: USAMRICD, Chemical Casualty Care Division, February 2007).

When appropriate, we refer to these two sources collectively as the USAMRICD Handbooks.

D. Research Approach for Chemical Agents

The following section is directly taken from IDA Paper P-5140[45] since it describes the same research approach used to derive the untreated and treated parameters for the five chemical agents in this report.

Chemical agent models for *AMedP-7.5* have three components: toxicity parameters, Injury Profiles, and MTOR tables. Each of the chemical agent chapters (3–5) describes the derivation of each of the three components. *AMedP-7.5* directly uses the toxicity parameters to estimate the number of individuals that follow the different Injury Profiles, and *AMedP-7.5* uses Injury Profiles to determine if and when the populations following each profile become casualties. Then, as warranted by the user's choice to use or ignore the effects of medical treatment, the methodology either follows the Injury Profiles or uses MTOR tables to determine casualty outcomes. The following three subsections define the three components and give an overview of how the models presented in subsequent chapters were developed. The final subsection discusses Haber's rule and toxic load modeling (TLM) and how the two relate to the analysis documented in the present paper.

1. Toxicity Parameters

For most agents, the required toxicity parameters are a median toxicity, or dosage,[46] that is expected to generate a specified effect in 50% of a population and a PS for each effect considered. Each set of toxicity parameters (median toxicity and PS) relates to a corresponding *peak* severity of symptoms, regardless of the elapsed time between challenge and the worst symptoms. Unless the supporting data for a specific agent indicate otherwise, four sets of parameter values are needed to reflect the mild, moderate, severe, and very severe/lethal effects (consistent with the Injury Severity scale in Table 1). *AMedP-7.5* relates each Injury Severity Level to a specific Injury Profile and uses the toxicity parameters to estimate the number of personnel that will follow each Injury Profile.

Median toxicities and PSs relate to *dosage*-based effects. Although toxicity should be expressed ideally as an amount per unit mass, the assumptions of a 70-kg human and a breathing rate of 15 L/min are built into reported toxicity parameter values, such that

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[45] Oxford et al., *Parameters for Estimation of Casualties from Phosgene, Chlorine, Hydrogen Chloride, Cyanide, Hydrogen Sulfide*.

[46] Sometimes referred to as concentration-time (Ct). The term *dosage* will be used in the present paper.

median toxicities are typically reported in units of milligram-minutes per cubic meter (mg-min/m^3), which, if multiplied by a breathing rate, gives units of mass (mg) for the assumed 70-kg person. Reported toxicity parameters are also intended to be applicable to a 2-minute exposure (which is relevant for the discussion in Subsection 2.D.4). PSs reported in the present paper are base 10 PSs, reported as probits/log(dose), as opposed to probits/ln(dose) for a base *e* PS.

The qualitative labels given to toxicity parameters differ slightly from the qualitative labels used in Table 1. Table 3 provides the necessary translation between the different sets of terms.[47]

Table 3. Qualitative Labels for *AMedP-7.5* Injury Severity Levels as Compared to Qualitative Labels for Toxicity Parameters

AMedP-7.5 **Injury Severity Label**	**Toxicity Parameter Label (Associated Symbols)**
Mild	Mild ($ECt_{50\text{-mild}}$ and PS_{mild})
Moderate	Moderate ($ECt_{50\text{-moderate}}$ and $PS_{moderate}$)
Severe	Severe ($ECt_{50\text{-severe}}$ and PS_{severe})
Very Severe	Lethal (LCt_{50} and PS_{lethal})

The ideal data source for estimating toxicity parameters and determining concentration thresholds—ethical considerations aside—is controlled human exposure under laboratory conditions. Typically, and for the five chemical agents in this paper, little such data exist. Some data on uncontrolled (accidental, suicidal, homicidal) exposure is available, but such data are, by their nature, incomplete. Typically, the dosage is not known. Toxicity studies in animals, including reporting the dosage, are relatively more plentiful.

However, there are several difficulties when animal model studies are used to estimate human toxicity. It is difficult to determine which animal is the best surrogate for humans in terms of toxic response and uptake of the toxin, and even the best surrogate cannot perfectly model a human. Thus, even after choosing a particular animal model, one must make assumptions to determine how to extrapolate from animal data to a human estimate. Unfortunately, no "correct" method of extrapolating is known, so the results can vary widely. Even if a "correct" method were known, it is important to be aware that "[n]o single value or number adequately addresses the reality of toxic effects from

[47] Since Very Severe effects are lethal in the absence of medical treatment, it is not inconsistent or incorrect to relate Very Severe to the median lethal dosage (concentration time) (LCt_{50}). The symbol LCt_{50} is used instead of $ECt_{50\text{-Very Severe}}$ because LCt_{50} is the symbol used in other literature.

exposure to a hazardous material" and that "[f]oundation data for all but a very few chemicals, is generally inadequate or unsatisfying."[48]

Where possible, we used toxicity estimates previously published by recognized experts—researchers at the ECBC and the CSAC. Their estimates are almost exclusively based on animal data, so the aforementioned considerations apply. Further, because the available ECBC/CSAC estimates are only for lethal and severe effects, we developed our own estimates for moderate and mild effects, and these estimates are also based primarily on animal data, so the aforementioned considerations again apply. Although it was necessary to develop moderate and mild toxicity parameter value estimates for the present paper, we do not recommend using these estimates for any other purpose.

2. Injury Profiles

The definition of Injury Profile, from *AMedP-7.5*, is given at the end of Subsection 1.A.1. Table 4 is an example Injury Profile, to familiarize the reader, taken from *AMedP-7.5*. Note that (1) the only time points included in Table 4 are those for which the Injury Severity Level changes for one of the Injury Profiles, and (2) the Injury Severity Level is modeled to change as a step function. Thus, for example, the GB Mild Injury Profile indicates Injury Severity Level 1 between 15 and 150 minutes, and an abrupt change to Injury Severity Level 0 at 150 minutes

Each Injury Profile is linked to a specific set of toxicity parameters (e.g., the GB Mild Injury Profile corresponds to the $ECt_{50\text{-}mild}$ and PS_{mild}), such that the toxicity parameters can be used to estimate the number of personnel that will follow each Injury Profile. A group of personnel following the same Injury Profile is referred to as an Injury Profile cohort. For an untreated casualty estimate, *AMedP-7.5* uses the Injury Profile to determine the final outcome for each Injury Profile cohort. For a treated casualty estimate, the Injury Profile is followed until the point at which medical treatment begins, and then the MTOR table (see Subsection 2.D.3) is used to determine the outcome.

Developing Injury Profiles is a difficult and somewhat subjective task that involves painstaking review of the open literature and controlled access archives, such as those at the Defense Technical Information Center (DTIC), which contains many historical records from chemical weapons research programs. For the agents in the present paper, the supporting data are from uncontrolled human exposures, controlled human exposures (the few for which data are available), and controlled animal exposures.

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[48] Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*.

Table 4. Inhaled GB Injury Profiles (from *AMedP-7.5*)

Time Point (Min)	GB Mild	GB Moderate	GB Severe	GB Very Severe
1	0	2	3	4
3	1	2	3	4
15	1	2	3	4[a]
150	0	2	3	
1920	0	1	2	
8640	0	1	1	

[a] According to the default value for $T_{death\text{-}CN\text{-}SL4}$, death would be modeled at this point.

One complication with using human data to develop Injury Profiles, however, is that Injury Profiles should describe what happens if *no treatment is provided*, whereas in reality, humans almost always receive treatment. Thus, some human data are not truly relevant for the purpose of developing Injury Profiles. If they are used anyway (due to a lack of other data), then the resulting models are somewhat biased.

One final note related to Injury Profiles is that each of the chapters begins with a qualitative description of the physiological effects of the agent (section A of each chapter), culminating in a table that links the different Injury Severity Levels with a set of associated symptoms. As was the case with similar tables reported in *AMedP-8(C)*, the symptoms listed in those tables "do not necessarily represent all [physiological] systems that might be impacted by exposure to [the agent]. Rather, they represent those systems that would be expected to cause individuals to seek medical attention soonest—those that would be expected to manifest symptoms earliest and at the highest severity. There may be other symptoms of lesser medical significance or severity which are not described."[49] Likewise, the Injury Profiles developed in later chapters are based on the symptom sets reported in the tables at the end of Section A of each of the chemical agent chapters (see Table 7, Table 14, and Table 22).

3. MTOR Tables

As the name suggests, MTOR tables account for two things: (1) the effects of medical treatment on casualty outcomes and (2) how casualty status is *reported*. The effects of medical treatment are incorporated into the models as probabilities of different outcomes as a function of the Injury Profile. The incorporation of the effects of medical treatment as probabilities of different outcomes depends on the supporting data. For GB, for example, Table 5 (reproduced from *AMedP-7.5*) shows the entire GB mild cohort being RTD on Day 2, whereas the GB severe cohort's RTD is split over three consecutive days.

[49] Curling et al., *Technical Reference Manual*, 23.

Table 5. GB MTOR (from *AMedP-7.5*)

Injury Profile	DOW	RTD	CONV
GB Mild	0%	Day 2: 100%	Day 8: 100%
GB Moderate	0%	Day 3: 100%	Day 15: 100%
GB Severe	0%	Day 5: 33.3% Day 6: 33.3% Day 7: 33.4%	Day 31: 100%
If casualties receive self-aid/buddy aid without further medical treatment:			
GB Very Severe, $X^{eff}_{GB,ih}$[a] < 100	0%	Day 15: 100%	0%
GB Very Severe, $X^{eff}_{GB,ih}$[a] ≥ 100	Day 2: 100%	0%	0%
If casualties receive self-aid/buddy aid and further medical treatment			
GB Very Severe, $X^{eff}_{GB,ih}$[a] < 165	0%	Day 15: 100%	0%
GB Very Severe, $X^{eff}_{GB,ih}$[a] ≥ 165	Day 2: 100%	0%	0%

[a] $X^{eff}_{GB,ih}$ is the Effective CBRN Challenge (dosage) of inhaled GB.

These differences are based on the supporting data as summarized in a previous IDA publication.[50]

As indicated by the supporting data, additional Injury Profiles may be created for an MTOR table. For example, for GB, self-aid/buddy aid *without* further medical treatment is modeled as preventing death for up to 3 × LCt_{50}, and self-aid/buddy aid *with* further medical treatment is modeled as preventing death for up to 5 × LCt_{50}. Thus, the Very Severe Injury Profile is split among several options, based on the treatment available and the Effective CBRN Challenge (see Table 5).

The difference between casualty *status* and casualty *reporting* is important—the main distinction being that casualties can change from one status to another on any given day, but their status can only be *reported* once per day (per the output time resolution of *AMedP-7.5*). Thus, *AMedP-7.5* incorporates the concept of reporting a casualty's most relevant status on a given day.[51] The rules for doing so are reproduced in Table 6.

The Table 6 rules are built into the MTOR tables derived in the present paper, such that they can be integrated as-is into *AMedP-7.5*. As an example of how the rules affect

[50] Curling et al., *The Impact of Medical Care*, 17–18.

[51] For example, medical planners need to know whether a person will require medical attention on a given day. Thus, the rules are tailored to ensure that if someone requires attention even for a fraction of that day, his/her status is reported such that a medical planner can account for the need (and translate that need into the resources required to meet it).

Table 6. *AMedP-7.5* Casualty Category Reporting Rules

Initial Category, Day X	Final Category, Day X	Report As, Day X	Report As, Day X + 1
WIA	KIA[a]	KIA	KIA
WIA	DOW	WIA	DOW
WIA	CONV	WIA	CONV
WIA	RTD	WIA	RTD
CONV	RTD	CONV	RTD

[a] By definition, this casualty category can only occur on Day 1.

MTOR entries, the supporting data indicated that recovery from mild GB symptoms would be complete and a casualty could RTD on Day 1,[52] but Table 5 does not report the casualties in the GB Mild row as RTD until Day 2, per the rule specified in the fourth row of Table 6. This approach allows the planner to allocate resources for that casualty for Day 1, since he will require medical attention for at least some portion of that day.

Similar to how Injury Profiles are derived, developing MTOR tables is difficult, somewhat subjective, and based on the information that can be found in the literature. In this case, human data tend to be more relevant since the goal is to capture the effects of medical treatment and most reports of human exposures involve medical treatment. As necessary, some animal data are used to fill in knowledge gaps. In some cases, injuries are sufficiently mild so that recovery occurs rapidly and independently of medical treatment. In such cases, the information reported in the MTOR is taken from the Injury Profile. For example, the GB mild Injury Profile (see Table 4) shows that the Injury Severity Level decreases to 0 at 150 minutes post-exposure. Casualties, therefore, become RTD on Day 1 (and as discussed previously, are *reported* as such on Day 2). This estimated time to RTD is not influenced by the availability of medical treatment.

4. Haber's Rule and TLM

Haber's rule is an approximation that states that for gas concentration C and exposure time t, any two groupings of C and t that have equivalent mathematical products produce equivalent toxic effects (K)—see Eq. 1.

$$\text{If } C_1 t_1 = C_2 t_2, \text{ then } K_1 = K_2 = K \tag{1}$$

Haber's rule is an approximation in any case in which the host eliminates the agent (the human body is able to eliminate many chemical agents). The longer the duration of

[52] Curling et al., *The Impact of Medical Care*, 16–17. Curling et al.'s results do not follow the outcome reporting rules specified here, so the table on page 15 of their document has numbers that are shifted by 1 day relative to Table 5.

exposure, generally the less accurate Haber's rule is thought to be. Reported toxicity parameters for the agents in the present paper are intended for exposures of 2-minute duration, so ideally, the toxicity parameter estimates generated as part of the analysis documented in the present paper must also be for 2-minute exposures (for consistency). However, much of the supporting data available for developing the chemical agent models relate to exposures of relatively long duration (even up to hours). Making use of such data requires some method of accounting for the human body's self-recovery mechanisms so that the data can be extrapolated to a 2-minute exposure.

One method of accounting for recovery mechanisms, and the method most commonly used within DOD, is TLM, which is essentially a "black-box" method of accounting for the fact that the human body detoxifies itself. It incorporates the fact of detoxification in a general sense, but the mathematical expression of that detoxification is entirely empirical. We believe that a better way of accounting for self-detoxification and recovery would be to create pharmacokinetic- and biochemistry-based models that account for factors such as the rate of detoxification likely being dependent on the total agent concentration (a general principle of chemistry) and the likely time-dependence of the rate of detoxification (due to the body's up-regulating expression of detoxification proteins). However, we bow to the realities that such models do not currently exist for the agents of interest here and that DOD appears to have little interest in developing such models. As such, the present paper will continue with a discussion of TLM and how it was used in the analysis described in later chapters.

As mentioned, TLM is an empirical model. Its most basic form[53] is shown in Eq. 2, which is similar to Eq. 1, except that it raises the concentration terms to the power of n, the toxic load exponent (TLE).

$$C_1{}^n t_1 = K = C_2{}^n t_2 \tag{2}$$

The TLE can be empirically estimated from binomial dose-response data, but the value derived is attached to the route of exposure and the specific endpoint that was measured. Thus, in theory, a TLE derived from inhalation lethality data should *not* be applied for estimating toxicity parameters for the inhalation mild endpoint, for example. However, out of expedience, a single TLE value is often applied across different effects but within the same route of exposure.[54] For each of the chemical agents of interest for

[53] Many other forms have been suggested and used, but the form shown here is appropriate for the present paper because the concentration data are single values, not time-varying values.

[54] For example, see U.S. Army Chemical School (USACMLS), *Potential Military Chemical/Biological Agents and Compounds*, II-17 and II-20. Note also that the same document shows a *different* value for GD inhalation mild than for GD inhalation severe/lethal (see page II-23) because data were available to generate a separate estimate.

the present paper, only one inhalation TLE estimate is available, and, in each case, it is applied across different levels of effect. The application of a TLE to a level of effect other than one from which it was derived introduces some additional level of uncertainty to the resulting toxicity parameter estimates.

Another source of uncertainty is that TLE values are derived from laboratory experiments in which *constant* concentrations are used for the challenge. Although researchers have begun testing the effect of non-constant concentrations,[55] the applicability of TLE values derived from constant concentration data to the more realistic scenario of wildly fluctuating challenge concentration is not clear. Given the current state of understanding, this uncertainty must be acknowledged but cannot be addressed in any quantitative way.

The specific way in which TLM was used in the present analysis is as follows. To attempt to compensate for supporting data being for relatively long duration exposures, we used the TLM concept to calculate an equivalent prompt dosage (EPD). The EPD is an estimate of the total dosage that, if inhaled during a 2-minute exposure,[56] would cause same physiological effects as a dosage that was inhaled over some other length of time. Rearranging Eq. 2 leads to Eq. 3, which calculates the concentration required (C_2) such that over some postulated exposure duration (t_2), the physiological effects, K, would be equal to those caused by a different exposure with known concentration (C_1) and exposure duration (t_1).

$$C_2 = C_1 \left(\frac{t_1}{t_2}\right)^{\frac{1}{n}} \tag{3}$$

Multiplying Eq. 3 by the postulated exposure duration, t_2, and setting t_2 equal to 2 minutes gives Eq. 4, which calculates the EPD. The use of these formulae is described in the agent-specific chapters.

$$C_2 \times 2 \text{ minutes} = \text{EPD} = C_1 \left(\frac{t_1}{2 \text{ minutes}}\right)^{\frac{1}{n}} \times 2 \text{ minutes} \tag{4}$$

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[55] Lisa M. Sweeney, Douglas R. Sommerville, and Stephen R. Channel, "Impact of Non-Constant Concentration Exposure on Lethality of Inhaled Hydrogen Cyanide," *Toxicological Sciences* 138, no. 1 (March 2014): 205–216.

[56] In theory, the EPD formulae shown in Eq. 4 could be used to extrapolate from any exposure time to any other exposure time. We do not recommend such extrapolations. In fact, if we had had any other option, we would have entirely avoided calculating or even discussing TLM and EPD.

3. Chemical Human Response Review: Ammonia (NH_3)

The objective of this chapter is to describe the development of a model of human response to NH_3 exposure and the effect of medical treatment on that model, as the basis of recommendations for implementing NH_3 casualty estimation into *AMedP-7.5*.

A. Physiological Effects of NH_3 Intoxication

NH_3 is the third most abundantly produced TIC in the world.[57] It is a strong irritant and corrosive that is toxic to humans in almost all exposure scenarios. Its odor threshold of 3.5–35 mg/m^3 (5–50 parts per million (ppm))[58] is sufficiently low to provide sensory warning of its presence. However, NH_3 causes olfactory fatigue or adaptation, making its presence difficult to detect when exposure is prolonged. Thus, the odor threshold may extend up to 37 mg/m^3 (53 ppm) according to the Agency for Toxic Substances and Disease Registry (ATSDR).[59]

1. Main Route for NH_3 Damage

The main route to damage caused by NH_3 is through the respiratory system. Although NH_3 rapidly enters the eye, causing local irritation and corrosive injuries, systemic absorption is not considered to be quantitatively significant.[60] Damage to the respiratory system when in contact with NH_3 is proportional to the depth of inhalation, duration of exposure, and concentration and pH[61] of the gas or liquid.[62] Following a short-term inhalation exposure, NH_3 is almost entirely retained in the upper nasal

[57] Igor Makarovksy et al., "Ammonia – When Something Smells Wrong," *Israel Medical Association Journal* 10, no. 7 (July 2008): 537.

[58] Sommerville et al., *Review and Assessment of Ammonia Mammalian Lethality Data*, 5-4.

[59] Agency for Toxic Substances and Disease Registry (ATSDR), "Toxicological Profile for Ammonia," last updated January 21, 2015, http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=11&tid=2; John E. Amoore and Earl Hautala, "Odor as an Aid to Chemical Safety: Odor Thresholds Compared with Threshold Limit Values and Volatiles for 214 Industrial Chemicals in Air and Water Dilution," *Journal of Applied Toxicology* 3, no. 6 (December 1983): 272–290.

[60] Makarovksy et al., "Ammonia – When Something Smells Wrong," 538.

[61] pH is a measure of the acidity or basicity of the solution.

[62] Ibid.

mucosa. The main clinical effects of large exogenous exposure to NH_3 include non-disabling reversible effects manifested by irritation to the eyes, throat, and nasopharyngeal region of the respiratory tract.[63] Inhalation of high concentrations of NH_3 or long-term exposure to NH_3 might cause severe damage to the respiratory tract, particularly in the tracheobronchial and pulmonary regions, and might lead to systemic absorption through the lungs.[64] The time during which symptoms begin to manifest is directly correlated to the exposure concentration. A higher exposure dose results in quicker appearance of symptoms. People who are able to escape the affected environment are usually not subjected to severe injuries. Furthermore, the absence of symptoms following inhalational exposure to NH_3 essentially rules out significant injury.

2. Clinical Manifestations of Acute NH_3 Exposure

The clinical manifestations of acute NH_3 exposure are usually immediate, and its toxic effects are mediated through its irritant and corrosive properties. NH_3 is an upper respiratory tract irritant, and its inhalation rapidly causes irritation to the nose, throat, and respiratory tract. Increased lacrimation and respiratory rate, coughing, and respiratory distress may occur. The retention of NH_3 at low concentrations in the nasal mucosa may protect against some lung effects. Substantial exposures to concentrated aerosols of ammonium hydroxide (NH_4OH) and elevated levels of NH_3 gas or anhydrous NH_3 fumes can cause burns at all depths in the oral cavity, nasopharynx, larynx, and trachea, together with airway obstruction, respiratory distress, and pulmonary edema.[65] Exposure to a massive concentration of NH_3 gas may be fatal within minutes, and asphyxiation may occur after exposure in poorly ventilated or enclosed spaces. Findings in fatal cases include extensive edema, full-thickness burns to the entire respiratory tract, purulent bronchitis, and greatly distended lungs.[66] The bronchial walls may be stripped of their epithelial lining.[67]

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[63] National Research Council, *Acute Exposure Guideline Levels for Selected Airborne Chemicals*, vol. 6 (Washington, DC: The National Academies Press, 2008), 60.

[64] Ibid.

[65] Lanny Garth Close, Francis L. Catlin, and Arnold M. Cohn, "Acute and Chronic Effects of Ammonia Burns on the Respiratory Tract," *Archives of Otolaryngology* 106, no. 3 (March 1, 1980): 151–158; Craig E. Amshel et al., "Anhydrous Ammonia Burns: Case Report and Review of the Literature," *Burns* 25, no. 5 (1 August 2000): 493–497.

[66] S. K. Price et al., "Fatal Ammonia Inhalation. A Case Report with Autopsy Findings," *South African Medical Journal* 64, no. 24, (December 3, 1983): 952–955; G. Woto-Gaye et al., "Death from Ammonia Poisoning: Anatomo-Pathologic Features," *Dakar Médical* 44, no. 2 (January 1999): 199–201.

[67] D. Ludec et al., "Acute and Long Term Respiratory Damage Following Inhalation of Ammonia," *Thorax* 47, no. 9 (September 1992): 755–757; Irving Kass et al., "Bronchiectasis Following Ammonia Burns of the Respiratory Tract: A Review of Two Cases," *Chest* 62, no. 3 (September 1972): 282–285.

Following ocular exposure, initial symptoms include an increased production of tears, a burning sensation, blepharospasm, conjunctivitis, and photophobia. At higher concentrations, corneal ulcerations, iritis, anterior and posterior synechia, corneal opacification, cataracts, glaucoma, and retinal atrophy may develop. Permanent eye damage can occur as a result of tissue destruction and elevations in intraocular pressure.[68]

Systemic effects following acute exposure to high concentrations of NH_3 include an elevated pulse and blood pressure, bradycardia, cardiac arrest, cyanosis, hemorrhagic necrosis of the liver, cerebral edema, seizures, and coma.

3. Mechanism of Toxicity and Pharmacology

NH_3 is extremely soluble in water and dissolves in the mucous fluid covering the mucous lining of the respiratory system to produce NH_4OH, a strong base. The reaction is exothermic in nature and may inflict significant thermal injury. NH_4OH causes severe alkaline chemical burns to the skin, the eyes, and especially the respiratory system. Mild exposure primarily affects the upper respiratory tract, while more severe exposure tends to affect the entire respiratory tract.

Tissue damage from NH_4OH is caused by liquefaction necrosis and penetrates far deeper than the damage caused by an equipotent acid. In the case of ammonium, the tissue breakdown liberates water, thus bringing about the conversion of NH_3 to NH_4OH. In the respiratory tract, this process results in the destruction of the cilia and the mucosal barrier, leading to infection. Moreover, secretions, sloughed epithelium, cellular debris, edema, and reactive smooth muscle contractions cause significant airway obstruction. Airway epithelium can regain barrier integrity within 6 hours after exposure if the basal cell layer remains intact. However, damaged epithelium is often replaced by granular tissue, which may be one of the causes of chronic lung disease following NH_3 inhalation injury.

Systemically absorbed NH_3 is well distributed throughout the body compartments and reacts with hydrogen ions, depending on the pH of the compartment to produce ammonium ions (NH_4^+). These ammonium ions are endogenously produced in the gut from the bacterial breakdown of nitrogenous constituents of food. Almost all of this endogenous ammonium is absorbed by passive diffusion from the intestinal tract before entering the hepatic portal vein. In the liver, ammonium ions are extensively metabolized to urea and glutamine. Consequently, the levels of NH_3 that reach the circulatory system are low.

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[68] Ann Welch, "Exposing the Dangers of Anhydrous Ammonia," *The Nurse Practitioner* 31, no. 11 (November 2006): 40–45.

NH_3 reaching the circulatory system is excreted by humans as urinary urea. Small amounts of NH_3 are excreted via urine. The average daily excretion for humans is approximately 2–3 μg, about 0.01% of the total body burden. Small amounts of unabsorbed NH_3 may also be excreted from gastrointestinal tract in the feces.

Table 7 summarizes the previous qualitative descriptions of the physiological effects after inhalation of NH_3. It is presented in a format amenable to use in *AMedP-7.5* and for analysis presented in this chapter.

Table 7. Association of NH_3 Injury Severity Levels with NH_3 Symptom Sets

Injury Severity Level	Set of Symptoms
0	No observable symptoms
1 (Mild)	Mild eye irritation, rhinorrhea, cough, sneezing, drooling, dyspnea, headache
2 (Moderate)	Tear production, burning sensation, blepharospasm, conjunctivitis, photophobia, more pronounced cough, pharyngitis, laryngitis, moderate throat irritation
3 (Severe)	Corneal ulcerations, iritis, anterior and posterior synechia, corneal opacification, cataracts, glaucoma; retinal atrophy, directly caustic to airway, laryngospasm, bronchospasm, chest pain, loss of consciousness
4 (Very severe)	Sloughing and necrosis of airway mucosa, severe chest pain, pulmonary edema, respiratory failure, cerebral edema, seizures, coma, death

Note for Table 7: Different chemical agents cause injury by different physiological mechanisms. Any apparent similarities between the symptom descriptions in this table and the symptom descriptions for another agent do not necessarily imply that the mechanisms of injury are the same.

B. Human Inhalation Toxicity Parameters for NH_3

The IDA team believes that the toxicity parameter estimates from CSAC are the best available, so we used them where possible. CSAC estimated that the median lethal dosage (concentration time) (LCt_{50}) is 67700 mg-min/m^3 for a 2-minute exposure in the healthy population.[69] Since CSAC did not report on the $ECt_{50\text{-severe}}$ value, we used the $ECt_{50\text{-severe}}$ value of 7800 mg-min/m^3 reported in ECBC-TR-856 for a 2-minute exposure in the healthy population.[70]

Although the CSAC report and ECBC-TR-856 use overlapping sources to derive the reported values, CSAC used six sources published post-1962 to calculate the weighted average of the PS while ECBC-TR-856 only used five of the six sources to determine the

[69] Sommerville et al., *Review and Assessment of Ammonia Mammalian Lethality Data*, 6-3.

[70] Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*.

weighted average of the PS. Therefore, the PS from the two sources differ. The PS for NH_3 reported by CSAC is 16.5, while the PS reported by ECBC-TR-856 is 17. The CSAC report on CK states that since severe effects and lethality follow the same toxic mechanism, the PSs should be the same.[71] This principle can also be applied to other agents and other levels of effect as long as the same toxic mechanism is still at work. Since CSAC has a more comprehensive set of sources and the toxic mechanism of NH_3 poisoning is independent of dosage, we assume the $ECt_{50\text{-severe}}$ PS is equal to the LCt_{50} PS reported by CSAC. Thus, for both levels of effect, we use 16.5 as the estimated PS.

Since the mechanism of NH_3 toxicity does not vary by severity of injury, we assumed that the mild, moderate, and severe PSs are equal to the lethal PS.[72] This assumption also helps avoid illogical results, such as two toxicity curves intersecting. For all levels of effect, we use 16.5 as the estimated PS.

Reports on accidental exposure to NH_3 that caused non-lethal effects are plentiful in the literature. However, none of the studies contained quantitative exposure data. Our literature review identified only a handful of reports on low-level toxicity study of NH_3 in humans that can be used for estimating mild and moderate toxicity parameters for this paper. Table 8 lists the human data that were gathered from four studies that we considered. Each study described the symptoms experienced by the exposed subjects when exposed to NH_3 over durations of $\geq$ 5 minutes. We were unable to acquire two of the studies (Industrial Bio-Test Lab (1973) and MacEwen et al. (1970)), but we obtained the data from a report by Sommerville, who described the symptoms experienced by the exposed individuals to the low levels of NH_3 as "mild."[73] Since most of the data have an exposure duration of $\geq$ 5 minutes and NH_3 has a toxic load exponent of greater than 1 (n = 2.0),[74] we deemed it necessary to use EPD calculations in an attempt to compensate for the data, which were only from relatively long durations of exposure. Calculating dosages without accounting for toxic load effects yields meaningless dose values when compared to the lethal and severe toxicity estimates.

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[71] D. R. Sommerville et al., *Review and Assessment of Cyanogen Chloride Mammalian Lethality Data and the Development of a Human Estimate*, CBRNIAC-1966387 (Aberdeen Proving Ground, MD: Chemical Security Analysis Center, Department of Homeland Security, October 2011), 6-11, FOR OFFICIAL USE ONLY.

[72] This principle is applied for several agents in Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*.

[73] Sommerville et al., *Review and Assessment of Ammonia Mammalian Lethality Data*, 4-2.

[74] Ibid., 6-2. This value is derived from lethal effects and then applied to other levels of effect.

Table 8. Relevant Non-Lethal Human Inhalational Exposures to NH_3

Source[75]	Inhaled Ct (mg-min/m^3)	Exposure Duration (Min)	Symptoms	Apparent Injury Severity Level
Industrial Bio-Test Laboratories, Inc.	112–175	5	Nasal dryness	0
	252–500	5	Nasal, eye, throat, and chest irritation, lacrimation	1
MacEwen, Theodore, and Vernot	210	10	Odor moderately intense to highly penetrating; irritation faint or not detectable	0
———	350	10	Highly penetrating odor, mild irritation	0–1
Verberk	1050	30	Moderately intense odor, moderate irritation to the eyes, nose, throat and chest; mild urge to cough; slight general discomfort	1
———	2100	60	Highly intense odor; moderate irritation to eyes, nose, throat, and chest; mild urge to cough; slight general discomfort.	1
———	1680	30	Highly intense odor; highly intense eye and nose irritation; moderate throat and chest irritation; mild urge to cough; moderate general discomfort	1
———	4200	120	Offensive odor; moderate irritation to eyes, nose, throat, and chest; mild urge to cough; mild general discomfort.	1
———	2310	30	Highly intense odor; moderate irritation to eyes, nose, throat and chest; mild urge to cough; moderate general discomfort	1–2

[75] Industrial Bio-Test Laboratories, Inc., "Irritation Threshold Evaluation Study with Ammonia," Report to the International Institute of Ammonia Refrigeration, Publication No. IBT 663-03161 (Northbrook, IL: IBT, March 23, 1973) (as cited in Sommerville et al., *Review and Assessment of Ammonia Mammalian Lethality Data*); J. D. MacEwen, J. Theodore, and E. H. Vernot, "Human Exposure to EEL Concentrations of Monomethylhydrazine," in *Proceedings of the 1st Annual Conference on Environmental Toxicology*, (Wright-Patterson AFB, OH: Aerospace Medical Research Laboratory, 1970), 355–363 (as cited in Sommerville et al., *Review and Assessment of Ammonia Mammalian Lethality Data*); M. M. Verberk, "Effects of Ammonia in Volunteers," *International Archives of Occupational and Environmental Health* 39, no. 2 (June 30, 1977): 73–81.

Table 8. Relevant Non-Lethal Human Inhalational Exposures to NH_3 (Continued)

Source[76]	Inhaled Ct (mg-min/m^3)	Exposure Duration (Min)	Symptoms	Apparent Injury Severity Level
———	3360	60	Highly intense odor; moderate irritation to eyes, nose, throat, and chest irritation; mild urge to cough; moderate general discomfort	1–2
———	2940	30	Highly intense odor; moderate irritation to eyes, nose, throat and chest; mild urge to cough; and moderate general discomfort	1–2
———	4620	60	Highly intense odor; moderate irritation to eyes, nose, throat and chest, mild urge to cough; and moderate general discomfort	1–2
———	6720	120	Highly intense odor; highly intense eye, nose, throat and chest irritation; moderate urge to cough; moderate general discomfort	2
———	5880	60	Highly intense odor; unbearable eye, nose, throat and chest irritation; moderate urge to cough; moderate general discomfort	2
———	9240	120	Highly intense odor; highly intense eye, nose, throat and chest irritation; urge to cough; general discomfort	2
———	11760	120	Highly intense odor; highly intense eye, nose, throat and chest irritation; highly intense urge to cough; and unbearable general discomfort	2–3
Silverman, Whittenberger, and Muller	5250	15	Nose and throat irritation, nasal dryness and stuffiness; excessive lacrimation; hyperventilation; unbearable – subjects unable to continue exposure to specified concentration	2–3

[76] L. Silverman, J. L. Whittenberger, and J. Muller, "Physiological Response of Man to Ammonia in Low Concentrations," *Journal of Industrial Hygiene and Toxicology* 31, no. 2 (March 1949): 74–78.

Table 9. Estimated Human EPDs from Table 8 Data

Source[77]	Inhaled Ct (mg-min/m^3)	EPD-Adjusted Dose (mg-min/m^3)	Apparent Injury Severity Level
Industrial Bio-Test Laboratories, Inc.	112–175	71–111	0
———	252–500	159–317	1
MacEwen, Theodore, and Vernot	210	94	0
———	350	157	1
Verberk	1050	271	1
———	2100	383	1
———	1680	434	1
———	4200	542	1
———	2310	596	1–2
———	3360	613	1–2
———	2940	759	1–2
———	4620	843	1–2
———	6720	868	2
———	5880	1074	2
———	9240	1193	2
———	11760	1518	2–3
Silverman, Whittenberger, and Muller	5250	1917	2–3

Using the EPD formula given in Subsection 2.D.4, we calculated the estimated human EPD (see Table 9). Based on the data, the estimated EPD range of 71–111 mg-min/m^3 caused exposed individuals to detect the odor and experience nasal dryness and, possibly, a faint irritation to the eyes, nose, throat, and chest. These resulting symptoms are less severe than Injury Severity Level 1 (mild) symptoms shown in Table 7; therefore, we conclude that exposure to a dose of $\leq$ 111 mg-min/m^3 will produce "no observable symptoms." The next estimated EPD range between 157 and 542 mg-min/m^3 caused NH_3-exposed patients to smell a highly intense odor and experience mild general discomfort, with moderate irritation to the eyes, nose, throat, and chest, and a mild urge to

[77] Industrial Bio-Test Laboratories, Inc., "Irritation Threshold Evaluation Study with Ammonia"; MacEwen, Theodore, and Vernot, "Human Exposure to EEL Concentrations of Monomethylhydrazine"; Verberk, "Effects of Ammonia in Volunteers"; Silverman, Whittenberger, and Muller, "Physiological Response of Man to Ammonia."

cough. These symptoms correlate to the Injury Severity Level 1 (mild) listed in Table 7. The estimated EPD range between 596 and 843 mg-min/m^3 caused NH_3-exposed individuals to experience moderate irritation to eyes, nose, throat, and chest, a mild urge to cough, and moderate general discomfort. We associated this range with an apparent Injury Severity Level between 1 and 2. The next estimated EPD range (868–1193 mg-min/m^3) is associated with an apparent Injury Severity Level 2 (moderate) and caused individuals to experience highly intense irritation to the eyes, nose, throat, and chest, a highly intense urge to cough, and moderate discomfort. The estimated EPD range between 1518 and 1917 mg-min/m^3 caused highly intense irritation to the eyes, nose, throat, and chest, a highly intense urge to cough, lacrimation, hyperventilation, and unbearable general discomfort. Such symptoms are correlated to an Injury Severity Level between 2 and 3.

Several options are available for using the six estimated EPDs that led to mild symptoms to estimate the $ECt_{50\text{-mild}}$. Seemingly reasonable options include the average of the values, the median of the values, and the average of the highest and lowest values. Since no metric is available for determining which strategy is best, we arbitrarily chose the latter, which gives the estimated $ECt_{50\text{-mild}}$ of 350 mg-min/m^3.

The three estimated EPDs that caused moderate symptoms can also be evaluated in the same way to estimate the $ECt_{50\text{-moderate}}$. The average of the highest and lowest values gives the estimated $ECt_{50\text{-moderate}}$ of 1000 mg-min/m^3 (rounded from 1031 mg-min/m^3). We recognize that this method of estimating dosage boundaries may not be the most accurate but found no other option. Therefore, as better data become available, the estimated $ECt_{50\text{-mild}}$ and $ECt_{50\text{-moderate}}$ should be updated accordingly.

Table 10 summarizes the set of median toxicities and PSs for Inhaled NH_3.

Table 10. Median Toxicities and PS for Inhaled NH_3

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	PS (Probits/Log(Dose))
NH_3 Very Severe	Lethal	67700	16.5
NH_3 Severe	Severe	7800	16.5
NH_3 Moderate	Moderate	1000	16.5
NH_3 Mild	Mild	350	16.5

[a] The median toxicity is an estimate for a 2-minute exposure.

C. NH_3 Injury Profiles

The corrosive and exothermic properties of NH_3 can result in immediate irritation and burns to several physiological systems of the body including respiratory, ocular, and upper gastrointestinal. The neurological and cardiac systems can develop symptoms over

time as the toxic effect of NH_3 progresses after an acute exposure. The following paragraphs describe the information used to determine the progression of NH_3 injury in the absence of medical treatment. The sources are primarily case reports based on accidents, government reports, and experimental studies.

A few sources,[78] some referencing other studies, generically describe mild and nondisabling NH_3 injury symptoms that correspond with the mild injury profile (e.g., "casualties with mild exposure present with pain and conjuctival and upper respiratory inflammation but no signs of respiratory distress"[79]). Lessenger noted that "patients presented with mild catarrhal symptoms including stinging of the eyes and mouth, pain on swallowing, and tightness of the throat. Vital signs in these patients were normal and the examination was normal with the exception of conjunctival and mucosal erythema. […] these people were sent home without any problems."[80] In low doses, the agent is primarily a centrally acting TIC and causes irritation when in contact with moist watery tissues of the central airways and the ocular system to rapidly form a strong alkaline solution.[81] Since *AMedP-7.5* defines time in its human response models as the time at which exposure ends, the onset of mild respiratory and ocular irritation occurs at time zero. Headache is another early symptom after mild NH_3 exposure,[82] although the accounts do not generally specify a time of onset. In the absence of specific timing information related to the onset of headaches, we assumed that the onset of headaches parallels that of the other physiological systems. Individuals recover quickly and are unlikely to have delayed or long-term adverse health effects after inhaling low doses of NH_3 if they are quickly moved into fresh air.[83] Such a qualitative statement poses a difficulty in quantifying the time to recovery after a mild exposure to NH_3. Since we found no other data that were specific to NH_3, we based this part of the NH_3 model on the Cl_2 model since both NH_3 and Cl_2 are pulmonary agents and follow similar mechanism of action. Therefore, the time at which respiratory symptoms recede from Injury Severity Level 1 to Injury Severity Level 0 in the NH_3 Mild Injury Profile is 6 hours.

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[78] Shirley D. Tuorinsky and Alfred M. Sciuto, "Toxic Inhalational Injury and Toxic Industrial Chemicals," in *Medical Aspects of Chemical Warfare*, ed., S. D. Tuorinsky, Textbooks of Military Medicine (Washington, DC: Office of the Surgeon General, Department of the Army, 2008), 339–370; James E. Lessenger, "Anhydrous Ammonia Injuries," VOLUME 3, NUMBER 3 *Journal of Agromedicine* 9, no. 2 (2005): 191–203; Makarovksy et al., "Ammonia – When Something Smells Wrong."

[79] Tuorinsky and Sciuto, "Toxic Inhalational Injury and Toxic Industrial Chemicals."

[80] Lessenger, "Anhydrous Ammonia Injuries," 197.

[81] Makarovksy et al., "Ammonia – When Something Smells Wrong."

[82] Britt-Marie Sundblad et al., "Acute Respiratory Effects of Exposure to Ammonia on Healthy Subjects," *Scandinavian Journal of Work, Environment & Health* 30, no. 4 (August 2004): 313–321.

[83] Makarovksy et al., "Ammonia – When Something Smells Wrong," 539.

Moderate symptoms are more severe irritation of the eyes, nose, and throat, more pronounced cough, chest pain, tightness of the chest, hoarseness, dysphagia, lacrimation, swelling of the eyelids, and conjunctival hyperemia.[84] These symptoms appear immediately or shortly after exposure. It has been noted that, "[t]he higher the exposure dose the sooner the symptoms will appear."[85] However, some symptoms, such as irritation of the eyes, nose, and throat, appear immediately upon exposure to NH_3.[86] Therefore, the onset of moderate respiratory and ocular symptoms is modeled at time zero since *AMedP-7.5* defines time in it human response model as the time at which exposure ends. The recovery time after a moderate exposure to NH_3 is not specifically quantified in the literature. However, the *Medical Aspects of Chemical Warfare* states, "patients show improvement within 48 to 72 hours, and patients with mild exposure could recover fully in this time."[87] Thus, the duration of moderate symptoms for respiratory and ocular symptoms is 72 hours. The literature does not indicate different levels of severity pertaining to the neurological system. Symptom progression and injury severity are assumed the same as that of the previous dosage range. For the NH_3 Moderate Injury profile, the moderate symptoms begin at Injury Severity Level 2 at time zero and recede to Injury Severity Level 0 in 72 hours.

Casualties in the next Injury Severity Level (severe) experience severe health effects with frank respiratory distress, productive cough, pulmonary edema, dysphagia, slight cyanosis, and intense dyspnea.[88] At such high dosage range, the exposure is great enough that NH_3 has reached the peripheral airway, resulting in peripheral effects, such as pulmonary edema, that begin between 2 and 24 hours after exposure. Before the onset of pulmonary edema, casualties will suffer respiratory and ocular symptoms, including chest pains, cough, intense dyspnea, lacrimation, and intense irritation of the eyes, nose, and throat. The effects of a large dose of NH_3 inhalational exposure cause immediate central effects that are followed by delayed peripheral effects. The USAMRICD Handbooks indicate that casualties who present with symptoms that lead to pulmonary edema before 6 hours after exposure will likely die even if medical treatment is provided, and casualties who present later than 6 hours after exposure will likely survive if immediate intensive

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[84] Tuorinsky and Sciuto, "Toxic Inhalational Injury and Toxic Industrial Chemicals," 356; Hurst et al., *Medical Management of Chemical Casualties Handbook*, 24; Maxwell Caplin, "Ammonia-Gas Poisoning Forty-Seven Cases in a London Shelter," *The Lancet* 238, no. 6152 (July 1941): 95–96.

[85] Makarovksy et al., "Ammonia – When Something Smells Wrong." 539.

[86] National Research Council, "Ammonia: Acute Exposure Guideline Levels," chap. 2 in vol. 6, *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (Washington, DC: National Academies Press, 2008), 59.

[87] Tuorinsky and Sciuto, "Toxic Inhalational Injury and Toxic Industrial Chemicals," 356.

[88] Ibid., 356; Caplin, "Ammonia-Gas Poisoning Forty-Seven Cases," 95.

medical care is provided.[89] We propose that individuals who are exposed to a severe level of NH_3 will immediately experience an onset of respiratory and ocular symptoms at Severity Level 2 that occurs at time zero. The symptoms then increase from Severity Level 2 to Severity Level 3 12 hours post-exposure to account for the onset of pulmonary edema. The change in severity levels at 12 hours was arbitrarily chosen as the midpoint between 2 and 24 hours of when peripheral effects would begin. For the recovery time, the *Medical Aspects of Chemical Warfare* states that "for patients with more severe respiratory symptoms, recovery can be expected within several weeks to months."[90] Thus, the IDA team models that the Injury Severity Level 3 recedes to Injury Severity Level 0 in 1 month (30 days).

At the NH_3 Very Severe Injury Profile, victims almost instantly become unconscious and have severe chemical burns of the face, eyes, mouth, and throat. Victims may regain consciousness or drift into coma and develop clinical and radiographic features of pulmonary edema and experience respiratory distress.[91] Our literature search revealed that an attempt was made to rescue (through medical treatment) all victims who were exposed to a lethal dose of NH_3; therefore, the time to death after NH_3 exposure is not substantiated. Thus, the Very Severe Injury Profile begins with instant Injury Severity Level 4 and death in 15 minutes.

Table 11 shows the complete NH_3 Injury Profiles for all four severity levels. Recognizing the arbitrary nature of some of the exact times used, we remind the reader that since *AMedP-7.5* uses 1-day time resolution, many of the arbitrary decisions will have no effect on estimates produced by *AMedP-7.5*.

D. The Effect of Medical Treatment on NH_3 Injuries

1. Principles of Medical Treatment

No antidote is available for NH_3 poisoning.[92] Depending on the rapidity of progression, symptomatic and supportive care may be able to save lives. The victim should be evacuated from the contaminated area immediately following exposure, and first aid treatment should be initiated promptly. The immediate care includes resuscitative support and decontamination as needed.

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[89] Hurst et al., *Medical Management of Chemical Casualties Handbook,* 31–32; Hurst et al., *Field Management of Chemical Casualties Handbook*, 60–63.

[90] Tuorinsky and Sciuto, "Toxic Inhalational Injury and Toxic Industrial Chemicals," 356.

[91] Kass et al., "Bronchiectasis Following Ammonia Burns"; Price et al., "Fatal Ammonia Inhalation. A Case Report"; Ludec et al., "Acute and Long Term Respiratory Damage."

[92] Makarovksy et al., "Ammonia – When Something Smells Wrong," 539.

Table 11. Inhaled NH_3 Injury Profiles

Time Point (Min)	NH_3 Mild	NH_3 Moderate	NH_3 Severe	NH_3 Very Severe
1	1	2	2	4
15	1	2	2	4[a]
60	1	2	2	
120	1	2	2	
180	1	2	2	
360	0	2	2	
720	0	2	3	
4320	0	0	3	
43200	0	0	0	

[a] Death is modeled to occur at this point, based on the default value of the parameter $T_{death\text{-}CN\text{-}SL4}$ in *AMedP-7.5*.

After inhalational exposure to NH_3, the patient should be moved into fresh air and provided humidified oxygen as soon as possible. Cardiopulmonary resuscitation and mechanical ventilation should be initiated if necessary. Aerosolized bronchodilators, such as salbutamol (Ventolin), can be administered as indicated to treat bronchospasm, together with corticosteroids and/or antibiotics. The patient should be kept under observation for at least 24–48 hours, and symptomatic treatment should be given as needed.[93] If the eyes have been exposed to NH_3, decontamination should be performed by irrigation with running water or normal saline for at least 10 minutes.[94] Local anesthetics and cycloplegics should be used to enable thorough irrigation and examination. The possibility of corneal damage exists, and, if damaged, topical antibiotics can be administered. A follow-up ophthalmologic examination 24 hours after initial exposure is recommended.[95]

2. Efficacy of Medical Treatment

Ideally, we would quantify the efficacy of medical treatment using a protection factor due to medical treatment (PF_{MT}), which can be calculated by taking the ratio of the median lethal dose (LD_{50}) inclusive of medical treatment to the LD_{50} without medical treatment, if such data are available. Other methods of calculating PF_{MT} may be useful, depending on the data available.

Literature reports on the treatment of NH_3 poisoning in humans are primarily clinical case reports. In most of these reports, a person is accidentally exposed to NH_3 gas. In

[93] Ibid., 540; Hurst et al., *Medical Management of Chemical Casualties Handbook*, 38.

[94] Makarovksy et al., "Ammonia – When Something Smells Wrong," 540.

[95] Ibid.

such cases, the dose cannot be directly compared to the proposed untreated dosages.[96] Case reports and the USAMRICD Handbooks do not provide any quantifiable description of the effect of medical treatment for NH_3 injuries for estimating PF_{MT}. Since no antidote is available, the dosages for untreated individuals are the same as the dosages for treated individuals. Based on the case reports, it is clear that medical treatment improves the prognosis of anyone exposed to life-threatening NH_3 dosages.

Since NH_3 is a common industrial and household chemical, it is the third most common chemical released accidentally from manufacturing or storage facilities in the United States.[97] Human accidental exposure to NH_3 via inhalation makes up most of the clinical case reports found in literature (see Table 12); however, using these reports for the treated models presents a few problems. First, available data on the NH_3 levels during an accidental release are limited since, in most cases, the air concentration was neither measured nor estimated. Second, in some cases, an explosion of the storage tank or fire in the nearby facilities accompanied the release of NH_3, which complicates the assessment of the damage caused by the gas leak itself.

Table 12. Clinical Case Reports of Human Exposure to NH_3

Source[98]	Exposure Type	Exposure Route	Outcome
Slot	Accident – Gas leak	Inhalation	1 died on day 30, 5 survived
Caplin	Accident – Gas leak	Inhalation	13 died, 34 survived
Levy et al.	Accident – Gas leak	Dermal, Inhalation	4 survived
Mulder et al.	Accident – Gas leak	Inhalation	Died after 6 hours
Kass et al.	Accident – Gas leak	Inhalation	2 survived, hospitalized for 13 and 27 days

[96] In most cases, the dose in unknown anyway, and we assigned cases to proposed untreated dosages based on reported symptoms and possibly based on the case outcome.

[97] Makarovsky et al., "Ammonia – When Something Smells Wrong," 542.

[98] Gerald M. J. Slot, "Ammonia Gas Burns: An Account of Six Cases," *Lancet* 232, no. 6015 (December 1938): 1356–1357 (as cited in Llewellyn Legters, *Biological Effects of Short High-Level Exposure to Gases: Ammonia* (Frederick, MD: Fort Detrick, U.S. Army Medical Research and Development Command, May 1980)); Caplin, "Ammonia-Gas Poisoning Forty-Seven Cases"; Donald M. Levy et al., "Ammonia Burns of the Face and Respiratory Tract," *Journal of the American Medical Association* 190, no. 10 (December 7, 1964): 873–876; J. S. Mulder and H. O. Van der Zalm, "A Fatal Case of Ammonia Poisoning," *Tydschrift voor Sociale Geneeskunde* 45 (1967): 458–460 (as cited in Llewellyn Legters, *Biological Effects of Short High-Level Exposure to Gases: Ammonia* (Frederick, MD: Fort Detrick, U.S. Army Medical Research and Development Command, May 1980)); Kass et al., "Bronchiectasis Following Ammonia Burns."

Table 12. Clinical Case Reports of Human Exposure to NH_3 (Continued)

Source[99]	Exposure Type	Exposure Route	Outcome
Walton	Accident	Inhalation	1 died, 6 survived
Sobonya	Accident – Explosion	Inhalation	Died on day 60
Montague et al.	Accident	Inhalation	14 survived
Price et al.	Accident – Gas leak	Inhalation	Died on day 85
Darchy et al.	Accident	Inhalation	Died on day 5
Dilli et al.	Abuse	Ingestion	Discharged on day 5

3. NH_3 MTOR Table

Table 13 is the MTOR table for NH_3 casualties. This table is derived from the Injury Profiles and RTD and DOW estimates from clinical case reports. See the paragraphs after Table 13 for discussion.

In the discussions that follow, which explain Table 13, the potential for administrative declaration of asymptomatic "casualties" or delaying RTD for additional monitoring is ignored, which is consistent with Subsection 1.B.1.a.

Table 13. NH_3 MTOR

Injury Profile	DOW	CONV	RTD
NH_3 Mild	0%	0%	Day 2: 100%
NH_3 Moderate	0%	0%	Day 4: 100%
NH_3 Severe	0%	0%	Day 8: 100%
NH_3 Very Severe	Day 31: 27%	Day 15: 36% Day 29: 37%	Day 91: 73%

Casualties of the NH_3 Mild group will recover spontaneously and be able to RTD after 6 hours. Caplin noted that the patients in the mild group were discharged from the hospital "after a few hours' rest in bed."[100] Therefore, since individuals in the mild cohort will recover sufficiently to RTD on Day 1, they are reported as RTD on Day 2 in the MTOR. The availability of medical treatment has no effect on recovery of the Mild Injury Profile.

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[99] M. Walton, "Industrial Ammonia Gassing," *British Journal of Industrial Medicine* 30, no. 1 (January 1973): 78–86; Richard Sobonya, "Fatal Anhydrous Ammonia Inhalation," *Human Pathology* 8, no. 3 (May 1977): 293–299; Terrance J. Montague and Arthur R. Macneil, "Mass Ammonia Inhalation," *Chest* 77, no. 4 (April 1980): 496–498; Price et al., "Fatal Ammonia Inhalation. A Case Report"; B. Darchy et al., "Acute Ammonia Inhalation," *Intensive Care Medicine* 23, no. 5 (May 1997): 597–598; D. Dilli et al., "A Non-Accidental Poisoning with Ammonia in Adolescence," *Child: Care, Health and Development* 31, no. 6 (November 2005): 737–739.

[100] Caplin, "Ammonia-Gas Poisoning Forty-Seven Cases," 95.

Individuals in the Moderate cohort will take longer to recover. Two of the clinical case reports listed in Table 12 describe patients in the moderate severity level that were given medical treatment. Walton describes an individual who had a light exposure to NH_3 that resulted in a burn on the left eye. The patient was treated with oxygen and eye wash and returned to work 3 days after exposure.[101] The second report describes five men who were exposed to a moderate level of NH_3 and experienced chest pain, cough, and dyspnea and were hospitalized for an average of 2 days.[102] Based on these two case reports, the availability of medical treatment has little effect on the recovery at this Injury Profile since, without treatment, the casualties will recover after 72 hours. Thus, casualties in this cohort will recover spontaneously and be able to RTD after 72 hours and are reported in the MTOR to RTD on Day 4.

NH_3-exposed individuals in the Severe cohort will take longer to recover, but, with supportive care, the recovery time will likely be shortened. Montague et al. describes nine patients with "abnormal chest findings manifested as rales, rhonchi, and wheezing" who were hospitalized for a mean duration of 6.3 days.[103] Without further data, the IDA team proposes that the availability of medical treatment will shorten the recovery time of individuals in the Severe cohort to 7 days, and they are reported as RTD on Day 8 in the MTOR.

The literature does not have any pertinent data to support an estimate of PF_{MT} to represent the effect of medical treatment on otherwise lethal NH_3 injuries in the NH_3 Very Severe cohort. Table 12 lists eight reports covering a combined 22 cases that would have been lethal without medical treatment. Based on these clinical case reports, the model estimates the efficacy of medical treatment by reducing the lethality rate for individuals in this cohort to 27%. For casualties who die when given medical treatment, their time until death is prolonged with treatment. The stated durations in the reports ranged between 6 hours and 85 days. Thirty days was arbitrarily chosen as the time until death with treatment and is reported in the MTOR as DOW on Day 31.

All of the remaining individuals in the Very Severe cohort were rescued when given medical treatment. Only 11 out of the 16 survivor cases reported the duration of the recovery. The duration was either described as the length of time spent in the hospital or the time until the individuals returned to work. In *AMedP-7.5*, the hospital discharge time is the estimate of when casualties become CONV, and the time that an individual can return to work is the estimate of when casualties become RTD. The clinical reports provide a range of the hospital discharge time to be between 13 and 27 days. To represent

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[101] Walton, "Industrial Ammonia Gassing," 81.

[102] Montague and Macneil, "Mass Ammonia Inhalation," 496.

[103] Ibid.

this range of hospitalization time without making an overly detailed model, we arbitrarily split the 73% modeled to survive between 14 and 28 days (weighted heavier at 28 days to match the data). The first and second groups of CONV are reported on Day 15 and Day 29, respectively, in the MTOR. Five cases reported the time that the individuals returned to work after recovery, and it ranged between 6 weeks and 6 months. To simplify the model, all survivors who are medically treated in the Very Severe cohort are modeled to RTD at 3 months and are reported in the MTOR as RTD on Day 91.

4. Chemical Human Response Review: Nerve Agents Tabun (GA), Soman (GD), and Cyclosarin (GF)

The objective of this chapter is to describe the development of a model of human response to nerve agents GA, GD, and GF exposures and the effect of medical treatment on the models, as the basis of recommendations for implementing GA, GD, and GF casualty estimation into *AMedP-7.5*.

A. Background

Nerve agents GA, GD, and GF are among the most toxic chemical warfare agents known. Together with GB,[104] they comprise the G-series nerve agents, thus named because German scientists first synthesized them. This series is the first and oldest family of nerve agents, and all the compounds in this series were discovered and synthesized during or before World War II (WW II), beginning with GA in 1936, followed by GD in 1944 and finally the more obscure GF in 1949.[105] The G-series nerve agents share a number of common physical and chemical properties. At room temperature, the G-series nerve agents are volatile liquids, making them a serious risk for two types of exposure: inhalation of nerve agent vapor and dermal contact with liquid nerve agent. Among the three, GD is the most volatile. From a military point of view, these agents qualify as nonpersistent agents, defined as "a chemical agent that when released dissipates and/or loses its ability to cause casualties after 10 to 15 minutes."[106] These nerve agent vapors are denser than air, making them particularly hazardous for persons in low areas or underground shelters. GD is colorless while GA ranges from colorless to brown. Both GA and GD smell fruity.

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[104] The human response parameters for GB are published in Curling et al., *Technical Reference Manual*, 61–97.

[105] Frederick R. Sidell, Jonathan Newmark, and John H. McDonough, "Nerve Agents," in *Medical Aspects of Chemical Warfare*, ed. S.D. Tuorinsky, Textbooks of Military Medicine, 155–219 (Washington, DC: Office of the Surgeon General, Department of the Army, 2008).

[106] Department of Defense, *Department of Defense Dictionary of Military and Associated Terms*, Joint Publication 1-02 (Washington, DC: Department of the Army, November 2010 (as amended through 15 October 2015)), 172.

Table 14 summarizes the qualitative descriptions for GA, GD, and GF in a format amenable to use in *AMedP-7.5* and for the analysis presented in this chapter.

Table 14. Association of GA, GD, and GF Injury Severity Levels with GA, GD, and GF Symptom Sets

Injury Severity Level	Set of Symptoms
0	No observable symptoms
1 (mild)	Miosis, rhinorrhea, transient chest tightness
2 (moderate)	Rhinorrhea, blurred vision or eye pain with sensitivity to light, mild headache, excessive airway secretions, induced cough, nausea, frequent cough
3 (severe)	Increased secretions and eye effects, vomiting, abdominal cramps, severe headache with anxiety and confusion, tight chest, twitching, weakness, diarrhea
4 (very severe)	Collapse and respiratory failure

B. Physiological Effects of Nerve Agent Intoxication

Nerve agents GA, GD, and GF act through similar mechanism of action—all three inhibit the proper functioning of the enzyme acetylcholinesterase (AChE) in its interaction with acetylcholine (ACh) by binding at the enzyme receptor sites and blocking hydrolysis. ACh is "the neurotransmitter of the neurons to skeletal muscle, of the preganglionic autonomic nerves, and of the post-ganglionic parasympathetic nerves."[107] In simple terms, ACh passes messages to the skeletal muscles and through the nervous system, thereby stimulating the system's reaction. The enzyme AChE breaks down (or hydrolyzes) the ACh, ending the stimulation trigger and allowing the muscle to relax. Nerve agents inhibit AChE function by binding to the enzyme's receptor sites, prohibiting the ACh compounds from binding to these now occupied sites. As a result, the enzyme is unable to hydrolyze the ACh, precluding the termination of the nerve signal. Because the stimulation trigger remains—and even intensifies—as ACh builds up in the system, the muscles remain constantly stimulated and are prevented from relaxing. This effect can eventually lead to death via several routes, including the failure of the central nervous system to stimulate respiratory drive, muscle fatigue leading to flaccid paralysis of the diaphragm, and asphyxiation due to constriction of the bronchial tubes combine with excessive secretions in the air passages. A brief summary of S/S follows to provide

[107] Frederick R. Sidell, "Nerve Agents," in *Medical Aspects of Chemical and Biological Warfare*, ed. Frederick R. Sidell, Ernest T. Takafuji, and David R. Franz, Textbook of Military Medicine, Part I: Warfare, Weaponry, and the Casualty, 129–179 (Washington, DC: Department of the Army, Office of the Surgeon General, 1997).

background material. More detailed discussions of these S/S are available in Sidell[108] and McDonough.[109]

In addition to the respiratory system, several physiological organs and systems are affected, including the eye, nose, mouth, pulmonary tract, gastrointestinal tract, skin and sweat glands, muscular system, cardiovascular system, and central nervous system.[110] "The magnitude and duration of a particular physiological effect is highly dependent on the level of agent exposure or dose of drug."[111]

The eye is sensitive to vapor or aerosols, with clinically and operationally important effects occurring at low levels. Ocular effects include miosis (constriction of the pupils), conjunctival injection (bloodshot eyes), dim or blurred vision, eye pain, impaired night vision, difficulty focusing, and appearance of eye inflammation.[112] The duration and severity of these effects depends on the exposure dose.

In addition to ocular effects, nerve agent exposure causes an increased level of secretions from the nose (rhinorrhea) and the sweat and salivary glands and in the pulmonary and gastrointestinal systems. In the gastrointestinal tract, these secretions may be accompanied by abdominal cramps, nausea, vomiting, and, in smaller segments of the population, diarrhea.[113]

In the pulmonary tract, an individual exposed to nerve agents may complain of a "tight chest," or a shortness of breath along with dyspnea (difficult or labored breathing) and increased bronchial secretions. The effect depends on the concentration and dose. As the dose increases, "respiration rapidly becomes gasping and irregular, and the victim can become cyanotic and totally apneic in a severe poisoning."[114] Symptoms experienced by individuals exposed to low doses may resolve spontaneously without medical interventions shortly after he or she is moved to cleaner air environments. At higher doses, medical interventions are required to reduce the effects and possible aid in ventilation.[115]

In the muscular system, the effects of nerve agents begin as stimulation at the muscle fibers and then progress to stimulation of individual muscles and muscle groups. The

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[108] Sidell, Newmark, and McDonough, "Nerve Agents."

[109] John H. McDonough, "Performance Impacts of Nerve Agents and Their Pharmacological Countermeasures," *Military Psychology* 14, no. 2 (2002): 93–119.

[110] Sidell, Newmark, and McDonough, "Nerve Agents," 170.

[111] McDonough, "Performance Impacts of Nerve Agents," 97.

[112] Ibid., 98–99.

[113] Ibid., 99–100; Sidell, Newmark, and McDonough, "Nerve Agents," 169–170.

[114] McDonough, "Performance Impacts of Nerve Agents," 100.

[115] Ibid.; Sidell, Newmark, and McDonough, "Nerve Agents," 173.

initial effects manifest as twitches, jerks, and fasciculations (visible contractions of small numbers of muscle fibers), leading to muscle fatigue. Following a large exposure, seizures or larger muscle group contractions can occur, causing flailing limbs and rigid hyperextension of the limbs and torso, and fasciculations can persist for days even when other symptoms have subsided.[116]

Exposure to nerve agents also causes neurological effects. These effects are dose dependent, with high doses correlating to increased percentages of individuals affected along with increased intensity and duration. Symptoms may include increased anxiety, tension, weakness, fatigue, forgetfulness, and irritability.

In summary, the symptoms of nerve agent exposure appear in several physiological systems of the body: respiratory, ocular, upper and lower gastrointestinal, muscular, and neurological. The effect of nerve agent poisoning is dependent on the exposure dose. A low vapor nerve agent exposure will cause immediate mild symptoms of ocular and respiratory irritations. As the exposure dose increases to moderate levels, ocular and respiratory symptoms intensify. The local S/S in the eye, nose, and airways caused by small to moderate amounts of vapor are due to the direct effect of the vapor on the organ and are not correlated to the blood AChE activity.[117] Finally, individuals exposed to a high dose of nerve agent may lose consciousness within less than a minute after exposure and exhibit convulsive jerking motions, copious secretions from the mouth and nose, and labored, irregular, and gasping breathing.[118]

C. Human Inhalation Toxicity Parameters for GA, GD, and GF

The relevant FM 3-11.9 and LLTP final report provide toxicity estimates for the three nerve agents. As stated in Subsection 2.C.2, we chose to use LLTP estimates instead of FM 3-11.9 estimates where there was conflict because the LLTP final report provides the most current parameter values. FM 3-11.9 estimated the LCt_{50}, $ECt_{50\text{-severe}}$, and $ECt_{50\text{-mild}}$ for GA to be 70 mg-min/m^3, 50 mg-min/m^3, and 0.4 mg-min/m^3, respectively, and estimated the PS to be 12.0 probits/log(dose) for the lethal level of effects and 10 probits/log(dose) for the severe and mild levels of effects. The LTTP final report estimated the LCt_{50}, $ECt_{50\text{-severe}}$, and $ECt_{50\text{-mild}}$ for GD to be 33 mg-min/m^3, 25 mg-min/m^3, and 0.2 mg-min/m^3, respectively. The same report also estimated the LCt_{50}, $ECt_{50\text{-severe}}$, and $ECt_{50\text{-mild}}$ for GF to be 41 mg-min/m^3, 31 mg-min/m^3, and 0.4 mg-min/m^3, respectively. For GD and GF, the LLTP final report estimated the PSs to be 12 probits/

[116] McDonough, "Performance Impacts of Nerve Agents," 100.

[117] Sidell, Newmark, and McDonough, "Nerve Agents," 165.

[118] Ibid., 168.

log(dose) for lethal and severe level of effects and 4.5 probits/log(dose) for the mild level of effect.

Since the parameter values in the LLTP final report are the most current and the physiological mechanism of toxicity is the same for the lethal and severe level of effects, we assumed that the lethal and severe PSs were the same for all three nerve agents. Therefore, the GA PS for $ECt_{50\text{-severe}}$ of 10 probits/log(dose) published in FM 3-11.9 is changed to 12 probits/log(dose) for this paper and for *AMedP-7.5*.

An individual suffering from mild effects after nerve agent exposure will primarily experience ocular effects and some mild respiratory symptoms. The physiological mechanism of toxicity for mild effects is not exactly the same as that for the other severity levels, and, therefore, the PS differs. Since the PS for $ECt_{50\text{-mild}}$ for GD and GF published in the LLTP final report is the most current, we assumed that the PS for $ECt_{50\text{-mild}}$ for GA was the same. Hence, the $ECt_{50\text{-mild}}$ for GA is changed from 10 probits/ log(dose) to 4.5 probits/ log(dose) for this paper and for *AMeP-7.5*.

The remaining question is, what values should be used for the moderate effect level for the three nerve agents? Since the primary mechanism of nerve agent toxicity does not vary among moderate, severe, and lethal severity levels, we assumed that the moderate PS is equal to the lethal and severe PSs for the three nerve agents.[119] The assumption also helps avoid illogical results such as two toxicity curves intersecting. For all levels of effect, except mild, we use 12 probits/log(dose) as the estimated PS.

To estimate the parameter for the three nerve agents, we first conducted a literature search for human exposures to any of the nerve agents that resulted in a moderate level of effects. The search revealed some case reports of human exposures; however, no quantifiable dose or dosage estimate is available because the exposure concentration and/or time are unknown. Further, most information on animal experiments relates to lethal and severe effects. With no other option, we arbitrarily set a value as the $ECt_{16\text{-moderate}}$ and use a PS of 12 probits/log(dose) to estimate the $ECt_{50\text{-moderate}}$ for the three nerve agents. For GA and GF, the $ECt_{16\text{-moderate}}$ is set at 1 mg-min/m^3 to give an $ECt_{50\text{-moderate}}$ of 1.2 mg-min/m^3. For GD, the $ECt_{16\text{-moderate}}$ is set at 0.5 mg-min/m^3 to give an $ECt_{50\text{-moderate}}$ of 0.6 mg-min/m^3. The final sets of median toxicities and PSs for inhaled GA, GD, and GF are summarized in Table 15, Table 16, and Table 17.

[119] This principle is applied for several agents in Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*.

Table 15. Median Toxicities and PSs for Inhaled GA

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	PS (Probits/Log(Dose))
GA Very Severe	Lethal	70	12
GA Severe	Severe	50	12[b]
GA Moderate	Moderate	1.2[c]	12[d]
GA Mild	Mild	0.4	4.5[e]

[a] Toxicity values from FM 3-11.9. The median toxicity is an estimate for a 2-minute exposure.

[b] Derived by IDA. Changed from 10 probits/log(dose) reported in FM 3-11.9 to 12 probits/log(dose) to be consistent with the more current published value for GD and GF in the LLTP report.

[c] Derived by IDA.

[d] Derived by IDA. Value matches the estimated PS for GD and GF reported in the LLTP report.

[e] Derived by IDA. Changed from 10 probits/log(dose) reported in FM 3-11.9 to 4.5 probits/log(dose) to be consistent with the more current published value for GD and GF in the LLTP report.

Table 16. Median Toxicities and PSs for Inhaled GD

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	PS (Probits/Log(Dose))
GD Very Severe	Lethal	33	12
GD Severe	Severe	25	12
GD Moderate	Moderate	0.6[b]	12[c]
GD Mild	Mild	0.2	4.5

[a] Toxicity values from the LLTP final report. The median toxicity is an estimate for a 2-minute exposure.

[b] Derived by IDA.

[c] Derived by IDA. Value matches the estimated PS for GD and GF in the LLTP report.

Table 17. Median Toxicities and PSs for Inhaled GF

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	Probit Slope (Probits/Log(Dose))
GF Very Severe	Lethal	41	12
GF Severe	Severe	31	12
GF Moderate	Moderate	1.2[b]	12[c]
GF Mild	Mild	0.4	4.5

[a] Toxicity values from the LLTP final report. The median toxicity is an estimate for a 2-minute exposure.

[b] Derived by IDA

[c] Derived by IDA. Value matches the estimated PS for GD and GF in the LLTP report.

D. GA, GD, and GF Injury Profiles

Different physiological systems of the human body, including respiratory, ocular, muscular, gastrointestinal, and neurological, are adversely affected by nerve agents. The different injury severity levels are associated with a set of S/S that illustrate the different

severity levels of the symptoms for a particular physiological system over time. The following paragraphs describe the information used to determine the progression of nerve agent injury in the absence of medical treatment. The open literature contains a few case reports[120] generically describing symptoms and recovery after exposure to a G-agent, typically by inhalation, but many are not applicable here because medical treatment was invariably provided. These case reports are considered later—in the discussion of the effect of medical treatment.

A few reports describe the symptoms of nerve agent poisoning after human accidental exposure to nerve agents, but these reports often lack dosage information. In addition, little human quantitative data are available to inform models of recovery time after nerve agent symptoms. Since the mechanism of action of all nerve agent poisoning in humans is the same, the IDA team assumes that the GA, GD and GF symptom progressions of each injury severity level are same and match the symptom progressions of each injury severity level for GB and VX after inhalational exposure. A report on 53 cases of accidental exposure supports such an assumption: "[s]ymptomology was quite consistent; there were no obvious differences between symptoms of those exposed to GA and those exposed to GB."[121]

Craig and Freeman[122] generically describe mild and non-disabling G-agent injury symptoms that correspond to the mild injury severity level after accidental nerve agent exposure. The authors summarized the nature and duration of mild S/S after low vapor exposure to nerve agents. However, the report does not disclose information on the concentration and duration of exposure. Miosis is noted to be the only consistent sign of toxicity, occurring in ~90% of the cases.[123] The degree of miosis and the speed of recovery were roughly proportional to the severity of total intoxication. Besides miosis, other early symptoms experienced by some patients include tightness of chest and rhinorrhea. These mild symptoms usually persist for only several hours.[124] To be consistent with the symptoms progression of GB and VX published in *AMedP-8(C)*, individuals exposed to low doses of nerve agents will be in Injury Severity Level 1 at 3 minutes post-exposure and recede to Injury Severity Level 0 in 2.5 hours.

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[120] A. B. Craig, Jr. and G. Freeman, *Clinical Observations on Workers Accidently Exposed to "G" Agents*, Medical Research Laboratory Report 154 (Edgewood Arsenal, MD: Medical Research Laboratory, 1953); Frederick R. Sidell, "Soman and Sarin: Clinical Manifestations and Treatment of Accidental Poisoning by Organophosphates," *Clinical Toxicology* 7, no. 1 (January 1974): 1–17; H. Nozaki et al., "Secondary Exposure of Medical Staff to Sarin Vapor in the Emergency Room," *Intensive Care Medicine* 21, no. 12 (December 1995): 1032–1035.

[121] Craig and Freeman, *Clinical Observations on Workers*, 4.

[122] Craig and Freeman, *Clinical Observations on Workers*.

[123] Ibid., 11.

[124] Ibid., 9–10.

Individuals exposed to any of the three nerve agents in the moderate injury severity profile should exhibit rhinorrhea, dimmed vision, blurred vision, ocular pain, mild headache, cough, and nausea. Sidell describes three individuals accidentally exposed to GB who experienced "very mild respiratory distress, marked miosis, with slight eye pain, rhinorrhea, and moderate increase in salivation, and scattered wheezes and rhonchi throughout all lung fields."[125] Respiratory distress had decreased for all of the patients shortly before arriving to the hospital, and symptoms generally improved over several hours; however, irritation to the eye and decreased vision to dim light continued even after being discharged 6 hours after arrival at the hospital. Complete recovery of AChE levels and ocular function took 2 months.[126] Craig and Freeman described three patients who were exposed to moderate levels of nerve agent and experienced irritation of the eyes, nose, and throat to include coughing, chest pain, frank shortness of breath, rhinorrhea, nausea, and mild neurological symptoms.[127] These three patients recovered within 24 hours after exposure.[128] In the same report, one patient who claimed to have been accidentally exposed to "G-agent" noted that his symptoms included "tightness of the chest, a cough productive of loose colorless material, an intermittent headache, rhinorrhea, excess salivation, excessive tearing, perspiration of the palms of the hands, photophobia, giddiness and nausea … examination revealed miosis … he complained of mild abdominal cramps and pain in the lower musculature."[129] This individual was free of most symptoms by 36 hours, and his pupils reacted normally by 48 hours post-exposure.[130] The symptom and duration summaries from the accidental exposure to nerve agents are consistent with injury profiles of two dosage ranges for GB (1–< 6.5 mg-min/m^3 and 6.5–< 12 mg-min/m^3) described in *AMedP-8(C)*. Both dosage ranges reach Injury Severity Level 2 immediately, and the lower of the two dosage ranges recedes from Injury Severity Level 2 to Injury Severity Level 1 in 1000 minutes (Day 1) while the higher dosage range recedes from Injury Severity Level 2 to Injury Severity Level 1 in 2880 minutes (end of Day 2). Since the change from Injury Severity Level 2 to Injury Severity Level 1 is pretty much meaningless *operationally*, we deemed that it was not necessary to retain the two distinct profiles. Therefore, we combined the two profiles, and Injury Severity Level 2 to Injury Severity Level 1 will occur in 32 hours (average of the two profiles). The GA, GD, and GF Moderate Injury Profiles are proposed to start at Injury Severity Level 2 immediately and recede to Injury Severity Level 1 in 32 hours.

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[125] Sidell, "Soman and Sarin: Clinical Manifestations and Treatment," 9.

[126] Ibid.

[127] Craig and Freeman, *Clinical Observations on Workers*, 66–67.

[128] Ibid.

[129] Ibid., 68.

[130] Ibid.

For *AMedP-7.5*, anyone following this profile will be at Injury Severity Level 2 on Day 2 but will be at Severity Level 1 on Day 3.

A data gap exists for the time to recovery for the Injury Severity Level 3 (severe). All data that involves human exposure at this severity level used medical treatment to rescue the intoxicated individuals, and, therefore, the time to recovery cannot be applied to this part of the analysis. At Injury Severity Level 3, the patient would experience symptoms in all the physiological systems. The *Medical Aspects of Military Warfare* provides two patients' accounts of their experience after exposure to a high dose of nerve agent produced severe symptoms. "One severely exposed individual later recalled to the authors that he noticed an increase in secretions and difficulty breathing, and another said he felt giddy and faint before losing consciousness. In both instances, the casualties were unconscious within less than a minute after exposure to agent vapor. When reached (within minutes) by rescuers, both were unconscious and exhibited convulsive jerking motions of the limbs; copious secretions from the mouth and nose; labored, irregular, and gasping breathing; generalized muscular fasciculations; and miosis."[131] With no other information, we used the same injury profile for inhaled GB with dosage range of 12–< 25 mg-min/m^3 in *AMedP-8(C)*. Hence, individuals who sustained severe injuries after being exposed to nerve agents would begin in Injury Severity Level 3 immediately and recede to Injury Severity Level 2 in 16.7 hours (1000 minutes). Patients will remain in Injury Severity Level 2 for 6 days and then recede to Injury Severity Level 1.

The final Injury Severity Level, Very Severe, suffers from the same issue as the previous Injury Severity Level. All patients severely intoxicated with nerve agents received immediate treatment that usually saved their lives. To be consistent with the GB and VX injury profiles in *AMedP-8(C)*, we modeled the GA, GD, and GF Very Severe Injury Profile as 100% lethal without treatment since the casualty remains at Severity Level 4 for more than 15 minutes.[132]

Table 18 summarizes the GA, GD, or GF Injury Profiles.

[131] Sidell, Newmark, and McDonough, "Nerve Agents," 168–169.

[132] NATO, *AMedP-8(C): NATO Planning Guide*, 4-4.

Table 18. Inhaled GA, GD, or GF Injury Profiles

Time Point (Min)	GA, GD, or GF Mild	GA, GD, or GF Moderate	GA, GD, or GF Severe	GA, GD, or GF Very Severe
1	0	2	3	4
3	1	2	3	4
15	1	2	3	4[a]
150	0	2	3	
1000	0	2	2	
1940	0	1	2	
8640	0	1	1	

[a] Death is modeled to occur at this point, based on the default value of the parameter $T_{death\text{-}CN\text{-}SL4}$ in AMedP-7.5.

E. The Effect of Medical Treatment on GA, GD, and GF Injuries

1. Principles of Medical Treatment

Medical treatment of nerve agent poisoning includes terminating the exposure, establishing or maintaining ventilation and circulation, and administrating antidotes such as atropine, oxime, and anticonvulsive therapy.[133] In addition to the antidote therapy, a pretreatment adjunct can also be used for some nerve agents. While supportive care is important to manage respiratory and cardiovascular symptoms to sustain life, antidote therapy is the only method that directly counteracts the inhibition of AChE to achieve a speedy and full recovery. The most critical factor in treating nerve agent casualties is the early recognition of the symptoms and the ability to provide rapid treatment.

a. Terminate the exposure/decontaminate patient

Perhaps the first and most important step in treating acute nerve agent poisoning is removing the patient from the source of exposure and decontaminating the patient. Decontamination is vital to eliminate further exposure to the casualty and to prevent medical personnel from becoming exposed. Except in cases where delaying treatment to decontaminate would result in a patient's immediate death, eliminating exposure should precede other treatment steps.

b. Summary of existing clinical antidotes

All countries worldwide use the same three therapeutic antidotes after nerve agent poisoning: an anticholinergic drug to counteract acute cholinergic crisis, an oxime to

[133] Sidell, Newmark, and McDonough, "Nerve Agents," 180; Fredrick R. Sidell, "Clinical Considerations in Nerve Agent Intoxication," in *Chemical Warfare Agents*, ed. Satu M. Somani (San Diego, CA: Academic Press, Inc., 1992), 175.

reactivate inhibited AChE, and a specialized anticonvulsant to treat or prevent seizures and resultant neuronal damage.[134] The most commonly administered anticholinergic is atropine. It binds to muscarinic postsynaptic receptors found on nerves, smooth muscle, glands, and the brain and prevents ACh from stimulating the synapse. Because atropine does not bind to nicotinic receptors, neuromuscular symptoms such as twitching and lack of coordination will persist. Oximes reactivate catalytic cholinesterase and simultaneously convert nerve agent into harmless, rapidly metabolized fragments. Oximes break the bonds between nerve agents and the enzyme, freeing up AChE to resume hydrolyzing ACh. Lastly, the anticonvulsant is used to treat seizures that may result from severe nerve agent exposure.[135] Some evidence suggests that atropine also plays a role in reducing nerve agent-induced seizures.[136]

The nerve agent antidotes issued to individual U.S. Service members consist of three Antidote Treatment Nerve Agent Auto-Injectors (ATNAAs) that each include 2.1 mg of atropine, 600 mg of pralidoxime chloride (2-PAM Cl) (the only oxime approved by the U.S. Food and Drug Administration (FDA) for use in the United States),[137] and one auto-injector containing 10 mg of the anticonvulsant diazepam. The recent switch to the single-needle ATNAAs resulted in a 50% reduction in time to administer the atropine and 2-PAM Cl over the formerly fielded MARK I Kits, which contained two separate auto-injectors for the two antidotes.[138]

The *Medical Management of Chemical Casualties Handbook* describes the procedures for self-aid and buddy aid on the battlefield. The instructions in the following

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[134] John H. McDonough and Tsung-Ming. Shih, "Atropine and Other Anticholinergic Drugs," in *Chemical Warfare Agents: Toxicology and Treatment*, 2nd ed., ed. Timothy C. Marrs, Robert L. Maynard, and Frederick R. Sidell (Chichester, UK: John Wiley & Sons, Ltd, 2007), 288; Jonathan Newmark, "Therapy for Nerve Agent Poisoning," *Archives of Neurology* 61, no. 5 (May 2004): 651.

[135] U.S. Army Medical Research Institute of Chemical Defense (USAMRICD), *Simapse 2.0 Nerve Agent Laboratory* (Aberdeen Proving Ground, MD: Chemical Casualty Care Division, 2009); McDonough and Shih, "Atropine and Other Anticholinergic Drugs"; Sidell, Newmark, and McDonough, "Nerve Agents."

[136] Tsung-Ming Shih, Tami C. Rowland, and John H. McDonough, "Anticonvulsants for Nerve Agent-Induced Seizures: The Influence of the Therapeutic Dose of Atropine," *Journal of Pharmacology and Experimental Therapeutics* 320, no. 1 (January 2007): 154–161; T.-M. Shih and J. H. McDonough, "Efficacy of Biperiden and Atropine as Anticonvulsant Treatment of Organophosphorus Nerve Agent Intoxication," *Archives of Toxicology* 74, no. 3 (May 2000): 165–172; Tsung-Ming Shih and John H. McDonough, "Organophosphorus Nerve Agents-Induced Seizures and Efficacy of Atropine Sulfate as Anticonvulsant Treatment," *Pharmacology and Biochemistry and Behavior* 64, no. 1 (September 1999): 147–153; M. Murphy et al., "Diazepam as a Treatment for Nerve Agent Poisoning in Primates," *Aviation, Space, and Environmental Medicine* 64, no. 2 (February 1993): 110–115.

[137] Sidell, Newmark, and McDonough, "Nerve Agents," 187.

[138] Ibid., 183.

extract are still current, although the next edition of the handbook will replace all references to the MARK I kits with the currently-fielded ATNAAs.

> The doctrine for **self-aid** for nerve agent intoxication states that if an individual has effects from the agent, he/she should self-administer one MARK I kit. If there is no improvement within 10 minutes, he/she should seek out a buddy to assist in the evaluation of his/her condition before further MARK I kits are given. If a buddy finds an individual severely intoxicated (e.g., gasping respiration, twitching, etc.) so that the individual cannot self-administer a MARK I kit, the buddy should administer three MARK I kits and diazepam immediately.[139]

According to *Medical Aspects of Chemical Warfare*, the amount of each antidote administered for definitive care depends on the severity of exposure and the response to treatment.

> In a conscious casualty with mild-to-moderate effects who is not in severe distress, 2 mg of atropine should be given intramuscularly at 5-minute to 10-minute intervals until dyspnea and secretions are minimized. Usually no more than a total dose of 2 to 4 mg is needed. In an unconscious casualty, atropine should be given until secretions are minimized (those in the mouth can be seen and those in the lungs can be heard by auscultation), and until resistance to ventilator efforts is minimized (atropine decreases constriction of the bronchial musculature and airway secretions).[140]

Administration of atropine to a severely exposed patient consists of "a 6 mg IM [intramuscular] loading dose followed by 2-mg increments until IV [intravenous] access is established."[141]

Since 2-PAM Cl and atropine are administered together via the ATNAA, the appropriate dose of 2-PAM Cl is somewhat tied to the dose of atropine. However, "because of the hypertensive effect of 2-PAM Cl, U.S. military doctrine states that no more than 2000 mg IV or three autoinjectors (600 mg each) should be given in 1 hour. If patients require additional treatment in the interim, atropine alone is used."[142] Although the therapeutic dosage of 2-PAM Cl is still undetermined, *Medical Aspects of Chemical Warfare* indicates that it is likely 15–25 mg/kg,[143] which is roughly equivalent to the amount from two to three ATNAAs administered to a 70-kg individual.

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[139] Hurst et al., *Medical Management of Chemical Casualties Handbook*, 141.

[140] Sidell, Newmark, and McDonough, "Nerve Agents," 184.

[141] Ibid.

[142] Ibid., 189.

[143] Ibid., 187.

U.S. doctrine states that if a nerve agent casualty requires three ATNAAs, one 10-mg autoinjector of diazepam is to be administered following the third ATNAA.[144] For a convulsing casualty, 30–40 mg of diazepam should be given to treat the seizures and prevent their return.

c. Pretreatment with pyridostigmine bromide (PB)

The U.S. military issues a pretreatment adjunct called PB to Service members in locations where a nerve agent attack is likely. PB is a reversible cholinesterase inhibitor.[145] PB reversibly inhibits a fraction (approximately 20%–40%)[146] of the large excess AChE in the human body, allowing soldiers to survive what would have been a lethal challenge of nerve agent. The PB bound fraction of AChE would be unavailable for the nerve agent to inhibit permanently and would become available if the patient was supported through the clinical crisis by the standard antidote therapy. Individuals are to take one 30-mg tablet of PB every 8 hours.[147] Once the patient has been exposed to the nerve agent, PB is contraindicated. PB does not obviate the need for the standard antidotes. It merely provides a countermeasure to individuals at risk of exposure to rapidly aging nerve agents.

The benefit of PB pretreatment is only realized if the aging time of the nerve agent-AChE complex is shorter than the time at which nerve agent antidotes are administered. Aging is a biochemical process that involves dealkylation of the nerve-agent-bound AChE complex, rendering the complex to be permanently resistant to treatment via oxime reactivation. Thus, the enzyme that has been bound to nerve agent and subsequently aged must be replaced by new synthesis of AChE by the body. Most nerve agents age slowly enough that this limitation is not crucial either tactically or clinically.

Table 19 summarizes the aging half time of GA, GD, and GF. Among the three G-series nerve agents, GD has the shortest aging half time, on the order of minutes, and thus is considered a rapid-aging nerve agent. Due to the short aging time of GD, pretreatment with PB is of paramount importance in anticipation of an attack. In the absence of PB pretreatment and after several half-times have elapsed, oxime therapy is useless in a patient poisoned by GD. At high dosages of GD, the patient cannot be rescued with just antidote therapy alone. The benefit of PB pretreatment after GD exposure is illustrated

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[144] Ibid., 190.

[145] A reversible cholinesterase inhibit means that the bond between PB and AChE is spontaneously broken, allowing the enzyme to resume its function of hydrolyzing ACh.

[146] Michael A. Dunn and Frederick R. Sidell, "Progress in Medical Defense Against Nerve Agents," *Journal of the American Medical Association* 262, no. 5 (August 1989): 651.

[147] Sidell, Newmark, and McDonough, "Nerve Agents," 202.

Table 19. Aging Half-Time of GA, GD, and GF

Nerve Agent	Red Blood Cell (RBC)-ChE Source	Aging Half-Time
GA	Human (in vitro)	13.3–14 hours
GD	Human (in vitro)	2–6 minutes
GF	Human (in vitro)	7.5–40 hours

Source: Frederick R. Sidell, Jonathan Newmark, and John H. McDonough, "Nerve Agents," in *Medical Aspects of Chemical Warfare*, ed. S.D. Tuorinsky, Textbooks of Military Medicine (Washington, DC: Office of the Surgeon General, Department of the Army, 2008), 198 (Table 5-8).

with non-human primate (NHP) studies that show monkeys that had no PB pretreatment were not well protected from GD by prompt administration of standard antidote therapy alone.[148] This method of treatment produced the typical protection ratio (PR) of 1.64.[149] However, use of PB pretreatment along with prompt post-challenge administration of standard antidote therapy resulted in vastly improved PR of > 40 (when compared to the control group) or > 24 (when compared to the group given the standard antidote therapy).[150] Therefore, Service members would be directed to use PB in anticipation of a GD attack. For the treated models, it is assumed that all personnel exposed to GD would have administered PB as a pre-exposure prophylaxis.

For GA and GF, the aging time is 13.3–14 hours and 7.5–40 hours, respectively.[151] Due to this long aging time, pretreatment with PB would not provide significant improvement in the treatment of individuals poisoned with GA or GF, and Service members would not be directed to use PB in anticipation of an attack with either nerve agent. Therefore, PB will not be considered as part of the course of pre-exposure prophylaxis for patients exposed to GA or GF.

d. Ventilation and circulation support

Supportive care to maintain ventilation and cardiovascular function is important for long-term survival and for the success of short-term antidote therapy. Patients with severe S/S will require assisted ventilation, oxygen, and suctioning of the copious secretions, in addition to clinical therapy. Animal studies have demonstrated that the effectiveness of clinical antidotes is greatly increased when ventilation is supplemented.[152] Wills[153]

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[148] Ibid., 199.

[149] Ibid.

[150] Ibid.

[151] Ibid.

[152] Ibid., 181; M. K. Christensen et al., "Resuscitation of Dogs Poisoned by Inhalation of the Nerve Gas GB," *Military Medicine* 119, no. 6 (December 1956): 377–386.

reported the unpublished findings of Muir and Clements that artificial ventilation of GB-exposed monkeys as a supplement to atropine therapy increased the PR more than 25 times over that of treatment with atropine alone. Christensen et al.[154] found that artificial respiration given to dogs, in addition to atropine, saved most of the animals when treatment was initiated within 4 minutes of post-exposure.

A complication of using atropine against nerve agent poisoning is when a patient experiences hypoxia, which may render the myocardium susceptible to arrhythmias. In these cases, atropine should not be given to an anoxic patient, but artificial respiration, oxygen, or other indicated measures should be carried out first to correct the anoxia.

Sustaining circulation is also essential to the successful treatment of nerve agent casualties, as the absorption of IM-injected antidotes relies on adequate blood flow through the muscles. "Atropine injected after [the precipitous fall in blood pressure] into a muscle no longer perfused with blood will be increasingly ineffective. Therefore, an important limiting factor in resuscitation is circulatory, in that the specific antagonist is dependent on the circulation for distribution."[155] As previously mentioned, since atropine administration to a severely hypoxic patient may cause cardiac arrhythmia, heart complications will need to be treated if they occur.

2. Efficacy of Medical Treatment

Literature reports on the treatment of nerve agent poisoning in humans are primarily clinical case reports. In most of these reports, a person accidentally inhales a nerve agent in a laboratory setting. In such cases, the dose is usually unknown, but we assigned cases to a dosage based on the reported symptoms and possibly based on the case outcome. Therefore, the cases are still useful for estimating the efficacy of medical treatment. In addition, the Iran-Iraq War produced thousands of Iranian battlefield nerve agent casualties,[156] and the terrorist attacks with GB in Tokyo resulted in thousands of civilian seeking medical care. Some reports also describe experiments on animal models, using various nerve agents through different routes of exposure and with different treatment

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[153] J. H. Wills, "Pharmacological Antagonists of the Anticholinesterase Agents," in *Cholinesterase and Anticholinesterase Agents*, ed. George B. Koelle (Berlin, Heidelberg: Springer-Verlag, 1963).

[154] Christensen et al., "Resuscitation of Dogs," 384.

[155] Ibid.

[156] Sidell, Newmark, and McDonough, "Nerve Agents"; J. Newmark, "The Birth of Nerve Agent Warfare: Lessons from Syed Abbas Foroutan," *Neurology* 62, no. 9 (May 11, 2004); U. Helm, "Treatment of Nerve Agent Poisoning by the Iranian Medical Services in the First Gulf War," (Bonn, Germany: University of Bonn, 1999).

regiments. Furthermore, the treatment of other organophosphorus compounds, used in pesticides, has been reported in the literature.[157]

a. Human cases

Table 20 provides a summary of articles reporting pertinent human exposures. Although the doses are unknown, based on the symptom descriptions, many of these cases were compared to the nerve agent casualty descriptions in *Medical Aspects of Chemical Warfare* and the injury profiles to approximate the severity of exposure and inform the duration of treatment and the expected time until patients RTD.

b. Animal studies

Although the human cases described in the previous section indicate a history of success treating even severe nerve agent casualties, it is anticipated that there is some dose above which treatment will cease to be effective. One measure of this upper boundary is the PR, defined as the LD_{50} for treated population divided by the LD_{50} for an untreated population exposure to the same challenge agent. Since human studies cannot be used to determine this value, animal studies are a logical surrogate.

Pretreatment with orally administered PB inhibits circulating RBC AChE by 20 to 45%, protecting the enzyme from being depleted when poisoned by a fast-aging nerve agent such as GD. As mentioned in Subsection 4.E.1.c, monkeys intoxicated with GD and given a combination of PB pretreatment along with prompt post-exposure administration of standard medical treatment resulted in a PR > 40. Other NHP studies support this finding. Dirnhuber et al.[158] showed that the combination of pretreatment and post-exposure standard therapy[159] was very effective against lethal effects of GD poisoning at 5–40 LD_{50} given subcutaneously. The treatment combination afforded complete protection against 20 LD_{50} of GA administered subcutaneously. The same study showed that

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[157] William, F. Durham and Wayland J. Hayes, "Organic Phosphorus Poisoning and Its Therapy," *Archives of Environmental Health* 5, no. 1 (1962): 21–47; Tatusji Namba and Kiyoshi Hiraki, "PAM (Pyridine-2-Aldoxime Methiodide) Therapy for Alkylphosphate Poisoning," *Journal of the American Medical Association* 166, no. 15 (April 12, 1958): 1834–1839; M. Balali-Mood and M. Shariat, "Treatment of Organophosphate Poisoning. Experience of Nerve Agents and Acute Pesticide Poisoning on the Effects of Oximes," *Journal of Physiology (Paris)* 92, nos. 5–6 (October–December 1998): 375–378.

[158] P. Dirnhuber et al. "Effectiveness of Pretreatment with Pyridostigmine in Protecting Rhesus Monkeys against Nerve Agent Poisoning," Chemical Defense Establishment Technical Paper (Wiltshire, England: Porton Down Chemical Defense Establishment, 1977).

[159] The oxime used in this study is P2S (pralidoxime mesylate), which is closely related to 2-PAM Cl—the chloride salt of the same compound. According to Durham and Hayes, "there appears to be no essential difference in the effects of the different salts of 2-PAM" (see Durham and Hayes, "Organic Phosphorus Poisoning and Its Therapy," 39).

Table 20. Reported Human Exposures to Nerve Agents or Organophosphorus (OP) Pesticides

Source[160]	Agent	Exposure Type	Exposure Route
Brown	GA, GB	Accident	Inhalational
Craig and Freeman	GA, GB	Accident	Inhalational, percutaneous
Craig and Cornblath	GA, GB, GD, GF, diisopropyl fluorophosphate (DFP)	Accident	Inhalation, percutaneous
Clanton and Ward	GB	Accident	Inhalational
Grob and Harvey	GB	Experiment	Oral, Intra-arterial, conjunctival
Durham and Hayes	Parathion	Accident	Inhalational, oral
Sidell	GB, GD	Accident	Inhalational, oral/dermal
Sidell and Groff	VX, GB	Accident	Oral, IV
Nozaki, Aikawa, et al.	VX	Terrorism	Percutaneous
Nozaki, Hori, et al.	GB	Terrorism	Inhalational
Okumura et al.	GB	Terrorism	Inhalational
Nakajima et al.	GB	Terrorism	Inhalational
Ohbu et al.	GB	Terrorism	Inhalational
Okudera et al.	GB	Terrorism	Inhalational
Balali-Mood and Shariat	Organophosphate (OP) pesticides	Accident	Oral
Helm	GA, GB	War	Inhalational
Okudera	GB	Terrorism	Inhalational
Newmark, 2004	GA, GB	War	Inhalational

Note for Table 20: Some cases are reported in more than one of the sources.

[160] E. C. Brown, *Effects of G Agents on Man: Clinical Observations*, Medical Division Report 158 (Edgewood Arsenal, MD: Medical Laboratory, 1948); Craig and Freeman, *Clinical Observations on Workers*; A. B. Craig, Jr. and M. Cornblath, *Further Clinical Observations in Workers Accidentally Exposed to "G" Agents*, Medical Research Laboratory Report 234 (Edgewood Arsenal, MD: Medical Research Laboratory, 1953); B. R. Clanton and J. R. Ward, *Case Report of a Severe Human Poisoning by GB*, Research Report No. 151 (Army Chemical Center, MD: Chemical Corps Medical Laboratories, December 1952); David Grob and John C. Harvey, "Effects in Man of the Anticholinesterase Compound Sarin (Isopropyl Methyl Phosphonofluoridate)," *Journal of Clinical Investigations* 37, no. 3 (March 1958): 350–368; Durham and Hayes, "Organic Phosphorus Poisoning and Its Therapy"; Sidell, "Soman and Sarin: Clinical Manifestations and Treatment"; Frederick R. Sidell and William A. Groff, "The Reactivatibility of Cholinesterase Inhibited by VX and Sarin in Man," *Toxicology and Applied Pharmacology* 27, no. 2 (February 1974): 241–252; Nozaki, Aikawa, et al., "A Case of VX Poisoning and the Difference from Sarin," *Lancet* 346, no. 8976 (September 9, 1995): 698–699; Nozaki, Hori, et al., "Secondary Exposure of Medical Staff to Sarin Vapor"; Tetsu Okumura et al., "Report of 640 Victims of the Tokyo Subway Sarin Attack," *Annals of Emergency Medicine* 28, no. 2 (August 1996): 129–135; Tamie Nakajima et al., "Sarin Poisoning of a Rescue Team in the Matsumoto Sarin Incident in Japan," *Occupational and Environmental Medicine* 54, no. 10 (October 1997): 697–701; Sadayoshi Ohbu et al., "Sarin Poisoning on Tokyo Subway," *Southern Medical Journal* 90, no. 6 (June 1997): 587–593; Hirosho Okudera et al., "Unexpected Nerve Gas Exposure in the City of Matsumoto: The First Rescue Experience of Sarin Gas Terrorism," *American Journal of Emergency Medicine* 15, no. 5 (September 1997): 527–528; Balali-Mood and Shariat, "Treatment of Organophosphate Poisoning"; Helm, "Treatment of Nerve Agent Poisoning by the Iranian Medical Services"; Hiroshi Okudera, "Clinical Features of Nerve Gas Terrorism in Matsumoto," *Journal of Clinical Neuroscience* 9, no. 1 (January 2002): 17–21; Newmark, "The Birth of Nerve Agent Warfare."

the PB pretreatment supported the standard antidote therapy and raised the subcutaneous LD_{50} of GA and GD in the rhesus monkey by a factor of greater than 20. In a later study[161] that was performed by the same authors, rhesus monkeys exposed to GD vapor for 15 seconds and pretreated with PB followed by post-exposure treatment with atropine, pralidoxime mesylate (P_2S), and diazepam raised the LCt_{50} by a factor of > 6 against GD poisoning.

The combination of pretreatment with PB and post-exposure standard therapy is also effective at rescuing NHPs exposed to GF intramuscularly. Koplovitz showed that 10 of 10 rhesus monkeys survived five LD_{50} of GF when given the combination PB pretreatment and post-exposure therapy.[162]

A 1997 study by Olson et al.[163] showed that two LD_{50} of GD given intramuscularly to exposed NHPs that were treated with only atropine and 2-PAM did not protect the monkeys. However, the same study revealed that six of seven GA-exposed rhesus monkeys survived more than 2 LD_{50} and that three of three GF-exposed monkeys survived more than 15 LD_{50} when treated with atropine and 2-PAM.[164] The study further confirms the importance of PB pretreatment along with post-exposure antidote therapy when lethal doses of GD are used.

3. GA, GD, and GF MTOR Table

Table 21 is the MTOR table for GA, GD, and GF casualties. The table is derived from the Injury Profiles and RTD and DOW estimates from clinical case reports. See the paragraphs after Table 21 for discussion.

Treatment for all three nerve agents will be assumed, as described in the doctrine, to include decontamination, artificial ventilation, and cardiovascular support if necessary and antidote therapy with atropine, 2-PAM Cl, and diazepam when required. Since PB treatment would be used in anticipation of exposure to GD only, PB pretreatment will only be modeled for GD. Thus, the Very Severe models shown in Table 21 will only apply for GD if PB pretreatment is also used; otherwise, any casualty in the Very Severe category will be modeled as KIA (not shown in Table 21).

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[161] P. Dirnhuber et al., "Effectiveness of Pyridostigmine Pretreatment in Protecting Rhesus Monkeys Against Inhaled and Intravenously Administered GD and GB," Chemical Defense Establishment Technical Paper (Wiltshire, England: Porton Down Chemical Defense Establishment, 1978).

[162] Irwin Koplovitz et al., "Evaluation of The Toxicity, Pathology, and Treatment of Cyclohexylmethylphosphonofluoridate (CMPF) Poisoning in Rhesus Monkeys," *Archives of Toxicology* 66, no. 9 (January 1992): 622–628.

[163] C. T. Olsen et al., "Efficacies of Atropine/2-PAM and Atropine/HI-6 in Treating Monkeys Intoxicated with Organophosphonate Nerve Agents," *International Journal of Toxicology* 16, no. 1 (January 1997): 9–20.

[164] Ibid., 13–14.

Table 21. GA, GD, and GF MTOR

Injury Profile	DOW	CONV	RTD
GA, GD or GF Mild	0%	Day 2: 100%	Day 8: 100%
GA, GD or GF Moderate	0%	Day 3: 100%	Day 15: 100%
GA, GD or GF Severe	0%	Day 5: 33.3% Day 6: 33.3% Day 7: 33.4%	Day 31: 100%
If casualties receive self-aid/buddy aid without further medical treatment:			
GA, GD,[a] or GF Very Severe, $X^{eff}_{GA,GD,GF,ih}$[b] < 3×LCt_{50}	0%	Day 15: 100%	0%
GB, GD,[a] or GF Very Severe, $X^{eff}_{GA,GD,GF,ih}$[b] ≥ 3×LCt_{50}	Day 2: 100%	0%	0%
If casualties receive self-aid/buddy aid and further medical treatment:			
GB, GD,[a] or GF Very Severe, $X^{eff}_{GA,GD,GF,ih}$[b] < 5×LCt_{50}	0%	Day 15: 100%	0%
GB, GD,[a] or GF Very Severe, $X^{eff}_{GA,GD,GF,ih}$[b] ≥ 5×LCt_{50}	Day 2: 100%	0%	0%

[a] The Very Severe models in this table will only apply for GD if PB treatment is also used; otherwise, any casualty in the Very Severe cohort will be modeled as KIA.

[b] $X^{eff}_{GA,GD,GF,ih}$ is the Effective CBRN Challenge of inhaled GA, GD, or GF.

In the following discussion, which explains Table 21, the potential for administrative declaration of asymptomatic "casualties" or delay of RTD for additional monitoring is ignored, which is consistent with Subsection 1.B.1.a.

For non-lethal exposures resulting in mild symptoms, Service members can relieve some symptoms with self-aid or buddy aid; however, since atropine is ineffective against miosis, mild ocular symptoms will remain for some time. Based on the Mild Injury Profile for GA, GD, and GF, casualties in the Mild cohort will experience mild symptoms on Day 1. Therefore, individuals in the Mild cohort will CONV on Day 1 and RTD after Day 7, so they are reported as CONV on Day 2 and RTD on Day 8 in the MTOR. Based on *Medical Aspects of Chemical Warfare*, for minimal exposures, "if liquid exposure can be excluded, there is no reason for prolonged observation,"[165] and patients can be returned to duty within a few hours. This information is confirmed by Brown,[166] who described three mild cases of accidental GA inhalation that all healed without therapy. After several hours of observation, the three patients were discharged with only mild-to-moderate bilateral miosis, one with headache, and another with mild cough and dyspnea. Nozaki et al.[167] reported mild symptoms among 13 emergency room doctors treating

[165] Sidell, Newmark, and McDonough, "Nerve Agents," 192.

[166] Brown, *Effects of G Agents on Man*.

[167] Nozaki, Hori et al., "Secondary Exposure of Medical Staff to Sarin Vapor."

victims of the Tokyo subway GB attacks. Fewer than half were treated with atropine (and one also received 2-PAM iodide), but all were able to continue working through their symptoms. The last symptom to resolve—dim vision—lasted from 2 to 12 hours in most patients, but did persist for 2 day in two patients. A summary of the treatment of 640 victims from the same attack was reported by Okumura et al.[168] Most of these patients (528) exhibited only mild symptoms and were released after a maximum of 12 hours of observations.

The *Medical Aspects of Chemical Warfare* recommends individuals in the GA, GD, or GF Moderate cohort "[to] be observed closely for at least 18 hours after the onset of signs and symptoms."[169] One case described by Craig et al.[170] states that the patient experienced diarrhea and vomiting, headache, coughing, rhinorrhea, and miosis after exposure to GB but that the diarrhea ceased by the morning of the third day and that the patient fully recovered by day 10 with atropine treatment. Grob and Harvey[171] describe experimental administration of GB in volunteers via oral, intra-arterial, and conjunctival exposure and comment that "the effects of sarin were very prolonged, lasting from several hours after the smallest effective doses to several days after doses which produced moderate symptoms."[172] These volunteers were treated only with atropine, and it is probable that the use of 2-PAM would have expedited their recovery times. In a later experiment, all volunteers, including those who experienced vomiting (a moderate symptom), had apparently recovered within 48 hours of the experiment. Therefore, patients exposed to dose/dosages that result in moderate symptoms will CONV for 2 days and are reported to CONV on Day 3 in the MTOR table. Full recovery from moderate injuries to nerve agent exposure will not occur until after 2 weeks, so Service members are reported as RTD on Day 15 in the MTOR table.

Individuals in the Severe Injury Profile cohort will take longer to recover, but, with treatment and supportive care, the recovery time will likely be shortened. Given the higher dosage range for this cohort, fewer human cases support the model. The best indication for the duration of recovery comes from a second group of patients described by Okumura et al.[173] as consisting of those with other symptoms in addition to the mild ocular symptoms previously discussed but not severe enough to require intubation or result in loss of consciousness. The 107 patients in this group likely contained those patients

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[168] Okumura et al., "Report of 640 Victims of the Tokyo Subway Sarin Attack."

[169] Sidell, Newmark, and McDonough, "Nerve Agents," 192.

[170] Craig and Freeman, *Clinical Observations on Workers*, 40–41.

[171] Grob and Harvey, "Effects in Man of the Anticholinesterase Compound Sarin."

[172] Ibid., 367.

[173] Okumura et al., "Report of 640 Victims of the Tokyo Subway Sarin Attack."

exposed to severe dose/dosage ranges and to the ranges for moderate exposure. After treatment with atropine and 2-PAM (and, in some cases, diazepam), all but two patients were discharged within 2 to 4 days, although, at the time of discharge, approximately 60% of patients still complained of eye symptoms and approximately 25% of patients complained of headaches. The mean duration in the hospital for this group was 2.4 days.[174] At the Severe Injury Profile cohort, the *Medical Aspects of Chemical Warfare* states that

> a soldier who has had signs of severe exposure with loss of consciousness, apnea, and convulsions, may have milder CNS [central nervous system] effects for many weeks after recovery from the acute phase of intoxication. Except in dire circumstances, return to duty during this period should not be considered for such casualties.[175]

Therefore, individuals who are experiencing severe symptoms will CONV on Day 4, 5, or 6 with equal probability and are reported to CONV on Day 5, 6, or 7 in the MTOR table. Since full recovery from a severe level of nerve agent exposure takes weeks, service members will RTD after 1 month and is reported to RTD on Day 31 in the MTOR table.

Exposures to doses/dosages that cause very severe effects will be 100% lethal without treatment since casualties remain at Injury Severity Level 4 for more than 15 minutes.[176] Based on the limited human cases and animal studies, it is reasonable to assume that with treatment, casualties at this dosage range would recover. As reported in the literature, of the 10 very severe human cases that lost consciousness and required artificial respiration after nerve agent exposure, 8 were effectively treated.[177] One of the two fatalities was unconscious and not breathing and was pronounced dead at the emergency room after not responding to 30 minutes of cardiopulmonary resuscitation (CPR). The second died of "severe hypoxic brain damage" 28 days post-exposure.[178]

To model the increased survivability with treatment, a PR like those derived from animal studies will be applied to humans, effectively extending the range of non-lethal exposures. The new threshold for lethality will be the previous upper boundary times the

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[174] Ibid., 131.

[175] Sidell, Newmark, and McDonough, "Nerve Agents," 194.

[176] North Atlantic Treaty Organization (NATO), *AMedP-8(C): NATO Planning Guide*, 4-4.

[177] Clanton and Ward. *Case Report of a Severe Human Poisoning by GB*; David Grob, "The Manifestations and Treatment of Poisoning Due to Nerve Gas and Other Organic Phosphate Anticholinesterase Com-pounds," *Archives of Internal Medicine* 98, no. 2 (August 1956): 221–239; Nozaki, Hori, et al., "Secondary Exposure of Medical Staff to Sarin Vapor"; Okumura et al., "Report of 640 Victims of the Tokyo Subway Sarin Attack"; Sidell, "Soman and Sarin: Clinical Manifestations and Treatment"; Sidell, Newmark, and McDonough, "Nerve Agents."

[178] Okumura et al., "Report of 640 Victims of the Tokyo Subway Sarin Attack," 132–133.

PR. As discussed in the previous section on animal studies, it is sensible to assume that a monkey would survive exposures of 20 LD_{50}. This same PR can be assumed to apply to humans for GA, GD, and GF inhaled exposures. However, the IDA team met with several SMEs[179] from USAMRICD in June 2015, and these SMEs pointed out that the PR based on the data from the Dirnhuber study is misleading. The antidotes were given 15 seconds after agent challenge, rather than at or after the onset of symptoms. In such a situation, one would expect the antidotes to perform far better than if they were given at the more operationally realistic time of when the symptoms began to appear. Thus, the NHP data to estimate the PR cannot be used.

After the meeting, the IDA team did additional literature search for NHP data that could be used to estimate the protection factor. Over 30 documents were identified that might be useful, but, in the end, none of these documents had data that could be used for this purpose. In order of decreasing frequency, these were the reasons the various data sets could not be used:

- Antidotes were given before the onset of symptoms (over 50% of reports).
- Dose of anticholinergic, oxime, and/or anticonvulsant was much higher than the doses fielded in autoinjectors by NATO forces.
- A specific set of antidotes used was not an anticholinergic, an oxime, and an anticonvulsant. Either a subset of the three or some additional drug was used
- Agent challenge was $1\times LD_{50}$ or $2\times LD_{50}$.

The USAMRICD personnel estimated that, for self-aid/buddy aid alone, a reasonable threshold dose for survival to be applied to GA, GD, and GF was $3\times LD_{50}$. The analogous estimate for self-aid/buddy aid plus further medical treatment was $5\times LD_{50}$. For GD, these thresholds would only apply if PB pretreatment was also used. Without PB, $1\times LD_{50}$ will be used. Although all present recognized that, in reality, the specific biochemistry of each agent will result in different thresholds per agent, the estimates of $3\times LD_{50}$ and $5\times LD_{50}$ were deemed suitable as generic estimates for the model. Everyone exposed to a degree less than the new thresholds will be modeled to survive but will require convalescent care for up to 2 weeks and will be reported to CONV on Day 15 in the MTOR table and will not RTD. Everyone exposed to amounts above these values will be modeled to die on Day 1 with either type of treatment and will be reported to DOW on Day 2 in the MTOR table.

As mentioned at the beginning of this section, PB pretreatment is only modeled for GD. Patients exposed to high dosages of GD cannot be rescued with antidote therapy alone. Thus, the model parameters for GD (see Table 21) assume that PB pretreatment is

[179] The USAMRICD SMEs included Dr. Charles Hurst, Mr. Timothy Byrne, and Dr. John McDonough.

used regardless of the type of post-exposure treatment used. However, if PB pretreatment is not given, casualties in the Very Severe cohort will be KIA[180] regardless of whether post-exposure antidote therapy or further medical treatment is provided. As shown in a NHP study, animals exposed to two LD_{50} of GD were not protected when treated with only atropine and 2-PAM.[181]

[180] To be classified as KIA, an individual's death must occur before reaching a MTF, and it is assumed that individuals will die if they have Severity Level 4 symptoms for 15 minutes before reaching the MTF and that casualties will reach the MTF 30 minutes after the end of exposure (see North Atlantic Treaty Organization (NATO), *AMedP-8(C): NATO Planning Guide*, Table A-53).

[181] Olsen et al., "Efficacies of Atropine/2-PAM and Atropine/HI-6 in Treating Monkeys," 12–13.

5. Chemical Human Response Review: Blister Agent—Lewisite (L)

The objective of this chapter is to describe the development of a model of human response to L exposure and the effect of medical treatment on that model, as the basis of recommendations for implementing L casualty estimation into *AMedP-7.5*.

A. Physiological Effects of L Intoxication

L, a vesicant similar to HD, contains organic arsenic. It primarily causes damage to the skin, ocular area, and respiratory system upon exposure. The major difference between the two types of vesicants is that L causes pain immediately whereas the effects of HD are delayed. A drop of liquid L on the skin causes irritation rapidly, and the vapor is immediately irritating to the eyes and airways. L might cause more severe symptoms than HD, but the immediate effects would likely signal that affected individual should leave the area of L contamination before severe effects are realized.

Topical exposure to vapor or liquid L is accompanied by immediate pain, compared to the delayed symptoms caused by HD, and, while the blisters produced by L exposure tend to be much more severe than those produced by HD, they heal faster.[182] In L lesions, the erythema is usually more distinct and displays a brighter red coloration than the erythema seen after exposure to HD. Erythema is evident within 15 to 30 minutes after exposure to L liquid and somewhat longer after vapor exposure.[183] The vesication stage is also reached sooner with L—occurring within 12 hours or less—than with HD, and the blisters are more sharply defined and increase in size more rapidly.[184] Liquid L exposure can penetrate the skin, subcutaneous tissue, and muscle, causing extreme edema and

[182] Max Goldman and Jack C. Dacre, "Lewisite: Its Chemistry, Toxicology, and Biological Effects," *Reviews of Environmental Contamination and Toxicology* 110 (1989): 75–115; Frederick R. Sidell et al., "Vesicants," in *Medical Aspects of Chemical and Biological Warfare*, ed. Frederick R. Sidell, Ernest T. Takafuji, and David R. Franz. Textbook of Military Medicine, Part I: Warfare, Weaponry, and the Casualty. Washington, DC: Department of the Army, Office of the Surgeon General, 1997.

[183] Goldman and Dacre, "Lewisite: Its Chemistry, Toxicology, and Biological Effects," 82; Sidell et al., "Vesicants," 293.

[184] Goldman and Dacre, "Lewisite: Its Chemistry, Toxicology, and Biological Effects," 82; Sidell et al., "Vesicants," 292–293.

necrosis. Although usually indistinguishable, the fluid contained in vesicles produced by L tends to be more opaque than that found in HD blisters.

Secondary infection after L exposure is less common compared to HD exposure,[185] which may be related to the fact that HD causes immune suppression whereas L does not. Also, the healing of L lesions is more rapid than the healing of lesions caused by HD exposure, thus decreasing the possibility of open wounds being exposed to infectious agents. In addition, the healing of L lesions is associated with little or no pigmentation.[186]

The ocular system is particularly sensitive to L vapor exposure; however, L is less likely to cause severe eye injury than HD vapor exposure because of the immediate irritation and pain after L exposure that results in blepharospasm, which effectively prevents further exposure.[187] L vapor exposure is still extremely irritating to the eyes, causing pain and lacrimation. Although the lacrimation and blepharospasm act, in a large degree, to protect from further exposure to the vapor, a sufficiently high dose causes irritation and pain to persist and, after a few hours, is followed by edema of the eyelids and conjunctivitis. Permanent damage is likely to result only in very high concentrations. As with HD, liquid L is capable of causing more severe damage to the eyes than L vapor exposure.[188] Pain, lacrimation, and blepharospasm appear immediately and are followed by edema of the eyelids, iritis, and conjunctivitis. In severe contamination, ulceration, necrosis, and secondary infection may lead to blindness or to permanent vision impairment.

L injuries to the respiratory tract have been reported to resemble the effects of HD. The regions within the pulmonary system that are affected by the inhalation of L vapors depend on the dose.[189] In general, the inhalation of L results in irritation of the nasal mucosa and upper airways and, at higher doses, the development of bronchitis is possible. However, in comparison to HD, L respiratory tract injury has several distinguishing characteristics. First, L has immediate effects on the mucus membranes, causing intense burning pain in the nasal mucosa, coughing, salivation, and sneezing. These symptoms usually subside within a few hours.[190] Second, the development of tracheobronchitis, pneumonia, and pulmonary edema are also more rapid with L, and such symptoms may persist for days.[191] Lastly, L appears to cause a much greater extent of pulmonary edema

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[185] Sidell et al., "Vesicants," 293.

[186] Ibid.

[187] Ibid.

[188] A. Feister et al. *Sulfur Mustard and Lewisite: Current Perspectives and Future Directions* (Frederick, MD: Fort Detrick, U.S. Army Medical Research and Development Command, 1989), 3-22.

[189] Hurst et al., *Medical Management of Chemical Casualties* Handbook, 112.

[190] Feister et al., *Sulfur Mustard and Lewisite*, 3-26.

[191] Sidell et al., "Vesicants," 293; Hurst et al., *Medical Management of Chemical Casualties* Handbook, 112.

than HD. Pulmonary edema is particularly noted after severe exposures and may be accompanied by pleural effusion that results in death.

While the local effects of L on epithelial tissues resemble those of HD, an individual is exposed to very high doses, in excess of those doses that produce incapacitating skin injuries. The systemic effects have been given the term "lewisite shock" and are caused by an increase in capillary permeability to plasma proteins, which results in an osmotic imbalance between the blood and tissue fluid.[192] All capillaries of the body are sensitive to L damage if the concentration is large enough. However, the lung capillaries are more sensitive to the action of L and so are more readily damaged. The effects of L shock include the development of pulmonary edema, followed by hemoconcentration, hypotension, depressed cardiac activity, and cyanosis. Death can occur as a result of either cardiovascular dysfunction or asphyxiation. High doses of L can also provoke gastrointestinal disorders with bloody diarrhea, hepatic disorders, and renal disorders.

Lower respiratory tract injury after exposure to high doses of L likely poses the most serious lethal threat. In severe cases, pulmonary edema may be sufficient to cause asphyxiation that leads to death. Individuals could alternatively die of secondary respiratory infections facilitated by damage to the respiratory epithelial lining. The last mechanism of death is due to increased permeability of the capillaries, which can lead to hemoconcentration and hypoproteinemia that result in depressed cardiac activity, cyanosis, and cardiac dysfunction.

1. Mechanism of Action of L Poisoning

Because L is an organic arsenic compound, its mechanism of toxicity differs from that of HD. The toxicity of L is due to its ability to bind to thiol groups that are essential for activity of a variety of enzymes.[193] The interaction with sulfhydryl groups of enzymes may result in inhibition of enzyme function because of the formation of stable cyclic structures with arsenic. It inhibits many enzymes—in particular, those with thiol groups such as pyruvic oxidase, alcohol dehydrogenase, succinic oxidase, hexokinase, and succinic dehydrogenase. As is the case with HD, the exact mechanism by which L damages cell has not been completely defined, but it is hypothesized that the ultimate mechanism of L toxicity appear to be energy depletion, which, in turn, results in cell death.

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[192] Sidell et al., "Vesicants," 293; Goldman, and Dacre, "Lewisite: Its Chemistry, Toxicology, and Biological Effects," 89.

[193] Constance M. Pechura and David P. Rall, eds., *Veterans at Risk: The Health Effects of Mustard Gas and* Lewisite (Washington DC: National Academy Press, 1993), 85.

2. Summary

The symptoms of L exposure appear in several physiological systems of the body—ocular, respiratory, and skin. Systemic intoxication can also occur after large exposure to L via inhalation or through the skin. At low dosages, L causes pain and blepharospasm on the ocular system and extreme irritation to the nasal area and upper airways. At progressively higher dosages, the respiratory irritation becomes chest pain, coughing, difficulty breathing, respiratory congestion, severe dyspnea, and potentially life-threatening pulmonary edema. Eye symptoms at higher dosage include severe eye irritation and inflammation, pain, and conjunctival erythema. Exposure to large dosages will cause systemic arsenic poisoning, typical early signs of which are vomiting and diarrhea. These actions can, in turn, cause severe fluid loss, which leads to circulatory disturbances including hypotension and shock. Other severe symptoms at higher dosage include organ congestion that may lead to hepatic or renal necrosis, hemoconcentration, depressed cardiac activity, and cyanosis. A mild exposure to L will cause the skin to be sensitive to touch. As the dosage increases, the skin will become sore and painful. Erythema and blisters will follow. Finally, at very high dosages, the skin lesions may result in necrosis and tissue sloughing.

Table 22 summarizes the qualitative descriptions of the physiological effects after exposure to L. It is presented in a format amenable to use in *AMedP-7.5* and for analysis presented in this chapter.

Table 22. Association of L Injury Severity Levels with L Symptom Sets

Injury Severity Level	Set of Symptoms
0	No observable symptoms.
1 (mild)	Irritation with eye pain; conjunctival erythema and/or edema; blepharospasm; mild shortness of breath; tight chest; cough; runny nose; skin sensitive to touch in crotch, armpits, and inside of elbow and knee joints.
2 (moderate)	Eye pain; irritation with conjunctival erythema and/or edema; blepharospasm; difficulty opening the eyes; sensitivity to light; frank shortness of breath; difficulty in breathing; wheezing breath; respiratory congestion; bronchorrhea; skin sore in crotch, armpits, elbow, and knee joints and painful when moving; red swollen skin; tiny blisters on hands and neck.
3 (severe)	Severe eye inflammation and pain leading to an inability to open the eyes; severe dyspnea; skin raw and painful in crotch, armpits, elbow and knee joints; red swollen body skin; large blisters on hands and neck.
4 (very severe)	Struggling to breathe or breathing stops completely; prostration; pulmonary edema; depressed cardiac activity; cyanosis; shock; skin sloughage after blisters or swollen skin.

B. Human Inhalation Toxicity Parameters for L

L human toxicity data are essentially nonexistent, and older reports estimate the L human toxicity parameters from old experimental animal studies. Many papers cite the 1946 Gates et al.[194] report, which summarizes the animal data used to derive the human toxicity parameters. It offers references to the animal studies performed in the 1940s or earlier; however, obtaining these studies to verify the data was not possible. The only collective toxicity values for L are published in FM 3-11.9, which provides the estimated toxicity parameters for L based on the toxicity recommendations for HD. Although L is a vesicant similar to HD, it has a completely different mechanism of toxicity. Another significant difference is that HD causes delayed injuries, while L results in rapid toxic effects. Due to the differences between HD and L and that no evidence to support that HD toxicity values can be used for L, the IDA team deemed it inappropriate to use the estimated toxicity parameters published in FM 3-11.9 as the parameters for L in this paper. The IDA team recommends further research to determine whether the proposed HD toxicity parameters can be used for L or whether new research to estimate toxicity values for L.

Since human inhalation toxicity parameters and PSs for L cannot be derived due to lack of data, the following sections will document the literature analysis performed by the IDA team on the injury profiles and effects of medical treatment for L.

C. L Injury Profiles

Although L and HD are both blister agents, the clinical progression of HD cannot be used to inform the clinical progression of L. The clinical manifestations of HD intoxication in humans are described in literature, and the injury profiles for HD poisoning are published in *AMedP-8(C)*[195] and will be revised in *AMedP-7.5*. However, the symptom progression of HD is a poor surrogate for L because the clinical symptoms of L poisoning begin much earlier and progress much faster compared to HD. Therefore, the injury profiles for L must be independent of HD.

Even though specific data are not available to model the injury profiles of the three physiological systems after L intoxication, the literature provides evidence that exposed individuals will not die immediately upon exposure to L; therefore, no casualties will be

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[194] Marshall Gates, Jonathan W. Williams, John A. Zapp, "Arsenicals," in *Chemical Warfare Agents, and Related Chemical Problems Part I-II*, vol. 1 of Summary Technical Report of Division 9, NRDS, ed. the Joint Research and Development Board Programs Division (Washington, DC: Office of Scientific Research and Development, 1946), declassified by DOD Memo 8/2/60, AD234270.

[195] Curling et al., *Technical Reference Manual*, 113–119; North Atlantic Treaty Organization (NATO), *AMedP-8(C): NATO Planning Guide*, A-21–A-25.

considered KIA.[196] L vapor, unlike HD vapor, is not insidious but gives adequate warning of its presence by irritation to the eyes, skin, and respiratory passages, which helps prevent serious injuries. Therefore, the mortality rate is expected to be low, and most casualties that die from L exposure succumb to respiratory tract injuries.[197]

Because L toxicity parameters cannot be estimated at this time, the L injury profiles will not be correlated to specific median toxicity values. Instead, the following subsections describe the symptom progressions of L in the three physiological systems—inhaled, ocular, and percutaneous—based on our literature analysis.

a. Inhaled L

As noted previously, one of the major differences between L and HD exposures is the time of effect. "Unlike mustard, Lewisite vapor and liquid causes immediate pain or irritation."[198] Overall, L injuries to the respiratory tract are similar to HD injuries but with immediate effects on mucus membranes, causing intense burning pain in the nasal mucosa, coughing, salivation, and sneezing. The initial mild symptoms generally abate within a few hours.[199]

Data on the histopathological lesions in the respiratory tract from inhaled L are available only from animals, but the reported lesions are generally very similar to those discussed for HD. The following describes the effects of HD on the respiratory tract:

> Damage to the respiratory tract involves acute edema, inflammation, and destruction of the airway epithelial. Depending on the dose, the destruction may be mild to severe. Severe damage includes destruction of the epithelium with subsequent formation of pseudomembranes, which may slough and obstruct the airway, resulting in death. In most cases, the injury is most severe in the larynx, trachea, and bronchi, with small bronchi less affected than large bronchi […] In some cases, presumably with high exposures, damage extends into the deeper alveolar regions, resulting in generalized edema of the lung.[200]

For prolonged exposure, large quantities of frothy mucus may be brought up. The effects of L vapor are so prompt and striking that exposed victims usually don a mask or exit the area before enough of the compound is inhaled to produce serious injury.[201] Systemic arsenic poisoning occurs after exposure to large doses, resulting in vomiting and

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[196] Feister et al., *Sulfur Mustard and Lewisite*; Gates, Williams, and Zapp, "Arsenicals."

[197] Feister et al., *Sulfur Mustard and Lewisite*, 3-46.

[198] Hurst et al., *Medical Management of Chemical Casualties Handbook*, 111.

[199] Feister et al., *Sulfur Mustard and Lewisite*, 3-26.

[200] Pechura and Rall, *Veterans at Risk*, 115.

[201] Hurst et al., *Medical Management of Chemical Casualties Handbook*, 112.

diarrhea approximately 30 minutes after exposure.[202] Severe exposures also cause the development of tracheobronchitis, pneumonia, and pulmonary edema, usually more rapid with L than with HD, and will persists for days.[203] L has been noted to cause more severe pulmonary edema than HD, especially after severe exposures.

b. Ocular L

Like HD, L vapor causes symptoms to appear in the eye before most other tissue. However unlike HD, eyes exposed to L vapor experience ocular effects immediately. L vapor causes pain, lacrimation, and blepharospasm immediately upon exposure. Although lacrimation and blepharospasm act, in a large degree, to protect from further exposure to the vapor, patients usually leave the area of contamination upon feeling the effects.

Although experience with L eye injuries is much less extensive, exposure to L vapor can produce some symptoms similar to those of exposure to HD vapor. Exposure of the eye to small quantities of L vapor can produce progressive lesion of the cornea, characterized by rapid tissue necrosis, pronounced edema, and intense exudation. If concentrations of L are high enough, the irritation and pain can persist and are followed by edema of the eyelids and conjunctivitis, which cause the eyes to be swollen shut after a few hours.[204] Permanent ocular damage is likely to occur from very high concentrations of L; however, such high concentrations might be difficult to achieve in the field.

In the 1940s, several studies[205] reported the ocular effects of L and HD vapor exposure in rabbits. Even though some ocular effects of L may be similar to those of HD, these studies revealed that the characteristics of the ocular lesions are quite different for L and HD vapor exposures. Table 23 summarizes the characteristics of the ocular lesions caused by L and HD.

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[202] Gösta Lindberg et al., *Basic Information on Lewisite: A Chemical Warfare Agent with Effects Similar to Mustard Gas*, FOA-R-96-00238-4.5-SE (Umea Sweden: Defense Research Establishment, Division of NBC Defense, 1997), 22.

[203] Feister et al., *Sulfur Mustard and Lewisite*, 3-26.

[204] Gates, Williams, and Zapp, "Arsenicals," 89; Hurst et al., *Medical Management of Chemical Casualties Handbook*, 112.

[205] Ida Mann, A. Pire, and B. D. Pullinger, "A Study of Lewisite Lesions of the Eyes of Rabbits," *American Journal of Ophthalmology* 29, no. 10 (October 1946): 1215–1222, 1222a, 1223–1227; Ida Mann, and B. D. Pullinger, "A Study of Mustard Gas Lesions of the Eyes of Rabbits and Men," *Proceedings of the Royal Society of Medicine* 35, no. 3 (January 1942): 229–244-7.

Table 23. Characteristics of L and HD Ocular Lesions

Lesion Type	L	HD
Onset of Ocular Action	Immediate and painful	No initial reaction; symptoms do not appear for some hours
Pupillary Reaction	Immediate strong miotic action	Not affected
Vascularization	Independent of the site of the primary lesion; occurs when sufficient dose reaches the cornea or limbus	Never occurs unless limbus is damaged
Vascular lesions	Not all lesions perforate; there are no relapses and no recurrent hemorrhages	Not all lesions perforate; tend to be chronic, to relapse and to show intra-corneal hemorrhages
Cholesterin and other lipid scars	Do not occur and no late breakdown	Follow some vascular lesions and subsequently breakdown
Perforation and loss of an eye	Caused by relatively small doses; perforation may occur within a few days without vascularization or later after the entry of blood vessels	Caused by relatively large doses; perforation never occurs as a primary lesions before the stage of vascularization
Edema	Edema of the lids and conjunctiva is immediate and severe; edema of the cornea is extreme in all but the smallest doses	Edema of the conjunctiva and cornea is present but not excessive
Iris and ciliary body	Early and severe involvement, followed by gradual depigmentation and shrinkage of the iris stroma	Relatively little involvement; no late effect on pigment
Vessel formation	Corneal vessels do not show the characteristic varicosities of HD vessels	Characteristic vessels form in cornea and conjunctiva

Source: Adapted from Constance M. Pechura and David P. Rall, eds., "Veterans at Risk: The Health Effects of Mustard Gas and Lewisite," 138.

c. Percutaneous L

L is a lipophilic substance, and, therefore, a primary route of entry into the body is absorption through the skin. Percutaneous absorption may be associated with systemic toxicity, manifested by pulmonary edema, diarrhea, agitation, weakness, hypothermia, and hypotension.[206] Systemic toxicity due to L exposure occurs more rapidly and is more severe compared to that of HD exposure.

[206] Pechura and Rall, *Veterans at Risk*, 164.

The action of L on the skin is more severe and more rapid than that seen after contact with HD. Upon exposure to L vapor, a burning sensation and pain occur rapidly, which serve as an early warning. Absorption begins immediately (5–10 minutes) and reaction occurs within 15–20 minutes, long before HD effects take place (latent period is at least 2 hours).[207] Vesication is observed within 2–3 hours with full lesions occurring between 12–18 hours.[208] The blister differs materially from that of an HD burn. Large, single coalescent blisters with sharply defined margins are filled with cloudy and opalescent fluid, and the surrounding erythematous zone seen routinely in HD poisoning is absent. At low dosage range, an itching and burning sensation can persist for several days, followed by healing in several weeks. As the exposure dosage of L increases, the onset of S/S is earlier, and the stinging and burning sensation is prolonged for up to 2 weeks, with a recovery time of at least 4 weeks.[209]

The histopathological changes in the skin after L exposure have been described in the literature:

> Unlike sulfur mustard exposure, Lewisite causes early and complete necrosis of the epidermis in humans. The necrotic process also involves the dermis where it is principally vascular in location. Capillary degeneration and perivascular leukocyte infiltration accompany Lewisite vesiculation.[210]

Table 24 summarizes the comparison of the percutaneous S/S after exposure to L and HD.

D. The Effect of Medical Treatment on L Injuries

1. Principles of Medical Treatment

Medical treatment for L poisoning involves symptomatic and supportive care similar to that after exposure to HD. An effective antidote—the British Anti-Lewisite (BAL) or 2,3-mercaptopropanol—was developed by biochemists at Oxford University in 1940 to counter the effects of L poisoning.[211] The United States first received BAL in 1941 and heavily studied and manufactured the antidote, which was widely distributed (56 million

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[207] Ibid.; Feister et al., *Sulfur Mustard and Lewisite*, 3-11.

[208] Ibid.

[209] Goldman and Dacre, "Lewisite: Its Chemistry, Toxicology, and Biological Effects," 84.

[210] Pechura and Rall, *Veterans at Risk*, 166.

[211] Joel A. Vilensky and Kent Redman, "British Anti-Lewisite (Dimercaprol): An Amazing History," *Annals of Emergency Medicine* 41, no. 3 (March 2003): 378–383.

Table 24. The Acute Effects of L and HD on the Skin[212]

S/S	L	HD
Sensation immediately post-exposure	Rapid burning and painful feeling	None
Absorption time	5–10 minutes	20–30 minutes
Latent period	12–50 minutes	2–12 hours
Erythema	Bright red, sharply defined area; painful pronounced edema, raised above healthy skin; expands slowly	Not very painful or edematous; itchy; expands rapidly to cover large area
Time of blister formation	2–3 hours	12–24 hours
Initial blister appearance	Large, possibly corresponding to area exposed	Fine vesicles on periphery of erythema, which eventually merge to form one larger blister
Development of blister	Inflammatory process peaks in 2–3 hours; regeneration begins in about 1 week	Inflammatory process peaks in 10–14 hours; new blisters may form over several days; regeneration begins in 2–4 weeks
Secondary infection of wound	Infrequent	Frequent
Healing time	3–4 weeks	1–4 months
Pigmentation after healing	No	Yes

Source: Adapted from A. Feister et al. *Sulfur Mustard and Lewisite: Current Perspectives and Future Directions* (Frederick, MD: Fort Detrick, U.S. Army Medical Research and Development Command, 1989).

tubes) to U.S. troops during WW II.[213] IM injection of BAL reduces the severity of systemic effects, and the use of BAL ointments prevents and greatly reduces the severity of lesions on the eyes and skin if these ointments are applied topically within minutes after exposure.[214] BAL binds to the arsenic of L more strongly than do tissue enzymes, thereby displacing L from the cellular receptor sites. Some unpleasant side effects associated with the use of BAL include hypertension and tachycardia. BAL is no longer manufactured in the United States as an antidote for L. BAL is used in medicine as a chelating agent for heavy metals and, therefore, is only stocked by hospital pharmacies and administered in hospitals. Nevertheless, BAL may find its use outside of the hospital setting if L is used against civilians or military forces. BAL should not be administered to individuals with a peanut allergy because BAL is dissolved and stored in peanut oil.

Without any antidote readily available to combat the effects of L poisoning in the battlefield, immediate decontamination after exposure is the only way to prevent and

[212] Feister et al., *Sulfur Mustard and Lewisite*, 3-11.

[213] Ibid., 379.

[214] Hurst et al., *Medical Management of Chemical Casualties Handbook*, 114–115.

minimize symptoms.[215] Since decontamination of the eyes and skin must be accomplished within minutes after exposure, this decontamination procedure is self-aid rather than medical management. After decontamination, lesions on the skin should be disinfected to avoid secondary infection, although secondary infection is less frequent after L poisoning than after HD poisoning.[216] Similar to HD treatment, antiseptic solutions, ointments, and creams can be applied to the skin and eyes of patients exposed to L.

If L gas is inhaled, the patient should be moved immediately from the source of exposure, and the respiratory function and pulse should be evaluated. Oxygen should be administered if dyspnea is observed, and ventilatory support should be provided as necessary. L shock causes hemoconcentration and hypotension, and, consequently, fluid balance should be monitored after exposure to a large dose of L.

2. Efficacy of Medical Treatment

No systematic evaluation of the efficacies of various treatments in humans has been conducted, but the effects of BAL treatment can be informed by a few animal studies.[217] Although BAL is no longer fielded in the military, it is still used in the hospital as a metal chelator. If an L threat is imminent, access to BAL may still be possible. Immediate decontamination reduces the local effects of L poisoning on the skin and in the eyes; however, it does little to prevent systemic intoxication by L. Therefore, patients exposed to high dosages of L require BAL treatment to survive.

One animal study shows the efficacy of BAL treatment in dogs after being exposed to L vapors.[218] The animals were exposed to lethal vapor concentrations of L, and, without treatment, the animals died of respiratory obstruction within 48 hours. However, administration of BAL, even when delayed until 90 minutes following exposure to L, resulted in marked reduction in mortality and prevented the development of pulmonary lesions. Without BAL treatment, 22 of 27 (> 80%) L-poisoned dogs died, while all L-poisoned dogs survived when BAL treatment was administered 30 minutes after

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[215] Ibid., 114.

[216] Feister et al., *Sulfur Mustard and Lewisite*, 3-12.

[217] H. E. Harrison et al., " Poisoning from Inhalation of the Vapors of Lewisite and Phenyldichlorarsine: Its Pathology in the Dog and Treatment with 2,3-Dimercaptopropanol (BAL)," *The Journal of Pharmacology and Experimental Therapeutics* 84, no. 4 (August 1946): 76–80; H. E. Harrison et al., "The Treatment of 2,3-Dimercaptopropanol (BAL) of the Systemic Toxic Effects of Skin Contamination with Lewisite and Phenyldichlorarsine," *The Journal of Pharmacology and Experimental Therapeutics* 84, no. 4 (August 1946): 81–84; William F. Hughes, "Treatment of Lewisite Burns of the Eye with Dimercaprol (BAL)," *Archives of Ophthalmology* 37, no. 1 (January 1, 1947): 25–41; I. Mann, A. Pirie, and B. D. Pullinger, "The Treatment of Lewisite and other Arsenical Vesicant Lesions of the Eyes of Rabbits with British Anti-Lewisite (BAL)," *American Journal of Ophthalmology* 30, no. 4 (April 1947): 421–436.

[218] Harrison et al., "Poisoning from Inhalation of the Vapors of Lewisite and Phenyldichlorarsine."

L exposure and 3 of 8 (38%) dogs died when BAL treatment was given to the animals 90 minutes after exposure to L.

Ocular effects due to L poisoning can be dramatically lessened with BAL ointment. Rabbits eyes poisoned with L can be rescued with 5% BAL ointment when applied 2 to 5 minutes after exposure to effectively prevent the development of serious ocular lesions.[219] The excellent therapeutic effect of BAL is due to its rapid penetration and withdrawal of toxic arsenical material from tissues before irreversible histological changes can develop. The efficacy of BAL ointment on eyes exposed to L is validated by Mann et al.,[220] where the application of BAL within 5 minutes to an eye contaminated with a destructive dose of L was successful in preventing the action of the L. A delay of BAL applications by 25 minutes also saved the function of the rabbit's eye but did not prevent partial permanent damage (vascular scars).

BAL can also counter skin lesions due to skin contamination with L. Prompt application of BAL solutions or ointment prevents these lesions completely.[221] BAL also prevents further development of erythema and causes rapid disappearance of initial redness. Harrison et al.[222] showed that L applied to dog skin in sufficient quantity is absorbed and causes systemic arsenic poisoning. The dogs were dosed with two LD_{50} or more of L. An application of BAL ointment on the local lesions of the skin after 30 minutes of exposure prevented further absorption of L, and an injection of a solution of BAL inhibited the toxic effects of the absorbed L. When 5% BAL ointment was solely applied to the contaminated skin, 7 of 8 (88%) animals died. A combination of 5% BAL ointment applied locally to the contaminated skin and 10% BAL in oil given intramuscularly to the L-poisoned dogs resulted in only 1 death out of 8 animals (13%). Treatment with BAL not only saved the animals from systemic action of L, but also resulted in increased urinary excretion of arsenic.

3. The L MTOR Table

Since deriving the injury profiles for inhaled, ocular, and percutaneous L vapor is not possible, the parameters for the MTOR also cannot be derived. The limited available animal studies illustrate the advantage of immediate decontamination, supportive care, and the use of BAL to shorten the recovery time of patients exposed to non-lethal dosages of L. BAL treatment is necessary to rescue patients after exposure to lethal dosages

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[219] Hughes, "Treatment of Lewisite Burns of the Eye."

[220] Mann et al., "The Treatment of Lewisite and Other Arsenical Vesicant Lesions."

[221] L. L. Waters and Chester Stock, "BAL (British Anti-Lewisite)," *Science* 102, no. 2659 (14 December 1945): 604.

[222] Harrison et al., "The Treatment of 2,3-Dimercaptopropanol (BAL) of the Systemic Toxic Effects of Skin Contamination."

of L. In these cases, a severely L-poisoned individual will die without BAL treatment. Based on animal studies, if BAL is administered in a timely fashion, an individual severely exposed to L will likely survive.[223] If data on symptom progressions of L poisoning become available, the untreated and treated models for L in the three physiological systems will be updated accordingly.

[223] Harrison et al., "Poisoning from Inhalation of the Vapors of Lewisite and Phenyldichlorarsine"; Harrison et al., "The Treatment of 2,3-Dimercaptopropanol (BAL) of the Systemic Toxic Effects of Skin Contamination."

6. Summary, Conclusions, and Recommendations

A. Summary

Over the past several years, IDA has developed a symptom-based methodology, now promulgated as NATO STANAG 2553, *Allied Medical Publication 8, NATO Planning Guide for the Estimation of CBRN Casualties (AMedP-8(C))*, to estimate the number, type, and timing of casualties from a CBRN attack. Since the promulgation of *AMedP-8(C)*, IDA has performed additional analyses to extend the capabilities of the *AMedP-8(C)* casualty estimation methodology. These efforts have included adding additional chemical and biological agents and developing a model to incorporate the effects of medical treatment on casualty estimates. IDA is now developing *AMedP-7.5*, which will replace *AMedP-8(C)* as NATO doctrine.

This paper describes the continued extension of chemical human response models and includes five additional agents—NH_3, GA, GD, GF, and L—that were specifically requested by OTSG. It includes proposed modeling parameters without and with consideration of medical treatment for each agent, together with the derivation of those values. It also identifies knowledge gaps and areas that require additional supportive data and supports transparency, reproducibility, and potential future refinement of the models by detailing the analytical choices that were made when estimating the parameter values.

B. Conclusions

The available data allow parameterization of models of human response to exposure to the selected chemical agents—excluding and including the effects of medical treatment. For some agents, medical treatment reduces the expected number of deaths and/or assists the recovery process, allowing for earlier estimated RTD.

For all five chemical agents, the supporting literature is not ideal. In the case of L, not enough data were available to derive the untreated and treated parameter values. This paper fully describes the derivation of all proposed model parameters, and, if new data become available, the models can be refined. Despite the uncertainties, we believe that the models derived in this paper represent current best estimates.

The models derived in this paper should be incorporated into *AMedP-7.5*. The content needed to incorporate the models into *AMedP-7.5* is presented within each agent-specific chapter.

Appendix A. Illustrations

Figures

Tables

Appendix B. References

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Appendix C. Abbreviations

2-PAM Cl	pralidoxime chloride
AC	hydrogen cyanide
Ach	acetylcholine
AChE	acetylcholinesterase
AEGL	Atmospheric Exposure Guideline Level
AMedP	Allied Medical Publication
ATNAA	Antidote Treatment Nerve Agent Auto-Injector
ATSDR	Agency for Toxic Substances and Disease Registry
BAL	British Anti-Lewisite
CBRN	chemical, biological, radiological, and nuclear
CBRNIAC	Chemical, Biological, Radiological, and Nuclear Defense Information Analysis Center
CG	phosgene
CK	cyanogen chloride
CL2	chlorine
CNS	central nervous system
CONV	convalescent
CPR	cardiopulmonary resuscitation
CSAC	Chemical Security Analysis Center
Ct	concentration time
DFP	diisopropyl fluorophosphate
DOD	Department of Defense
DOW	died of wounds
DSWA	Defense Special Weapons Agency
DTIC	Defense Technical Information Center
ECBC	Edgewood Chemical Biological Center
ECt_{50}	median effective dosage (concentration time)
EEE	Eastern equine encephalitis
ERPG	Emergency Response Planning Guideline
EPD	equivalent prompt dosage
FDA	U.S. Food and Drug Administration
FM	Field Manual
GA	tabun
GB	sarin
GD	soman
GF	cyclosarin
H_2S	hydrogen sulfide
HD	sulfur mustard
IDA	Institute for Defense Analyses
IDLH	Immediately Dangerous to Life and Health

IM	intramuscular
IV	intravenous
KIA	killed in action
L	lewisite
LCt_{50}	median lethal dosage (concentration time)
LD_{50}	median lethal dose
LLTP	Low-Level Chemical Warfare Toxicology Research Program
MACW	Medical Aspects of Chemical Warfare
MTF	Medical Treatment Facility
MTOR	medical treatment outcome reporting
NATO	North Atlantic Treaty Organization
NH_3	ammonia
NH_4OH	ammonium hydroxide
NHP	non-human primate
NRC	National Research Council
NTMS	NATO Terminology Management System
OP	organophosphate
OTSG	Office of the Surgeon General
PB	pyridostigmine bromide
PF	protection factor
P_2S	pralidoxime mesylate
PF_{MT}	protection factor due to medical treatment
ppm	parts per million
PR	protection ratio
PS	probit slope
RBC	red blood cell
RTD	return to duty
S/S	signs and symptoms
SME	subject matter expert
STANAG	Standardization Agreement
TEEL	Temporary Emergency Exposure Limit
TIC	toxic industrial chemical
TLE	toxic load exponent
TLM	toxic load modeling
TR	Technical Report
U.S.	United States
USAMRICD	U.S. Army Medical Research Institute of Chemical Defense
VX	O-ethyl-S-(2-diisopropylaminoethyl)methyl phosphonothioate
WEE	Western equine encephalitis
WIA	wounded in action
WIA(1)	Wounded in action (Severity Level 1 (“Mild”) or greater)

WIA(2)	Wounded in action (Severity Level 2 (“Moderate”) or greater)
WIA(3)	Wounded in action (Severity Level 3 (“Severe”) or greater)
WW II	World War II

Symbols

$T_{death\text{-}CN\text{-}SL4}$	The time at Injury Severity Level 4 sufficient to cause death from untreated chemical, nuclear blast, or nuclear burn injuries
T_{MTF}	The time required for an individual who is WIA to reach a MTF
$X^{eff}_{GA,ih}$	Effective CBRN Challenge (dosage) of inhaled GA
$X^{eff}_{GD,ih}$	Effective CBRN Challenge (dosage) of inhaled GD
$X^{eff}_{GF,ih}$	Effective CBRN Challenge (dosage) of inhaled GF

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Health Care Operations, (DASG-HCO-G34)
7700 Arlington Blvd, Ste 5143
Falls Church, VA 22042-5143
harry.m.stewart4.mil@mail.mil

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14. ABSTRACT

The U.S. Army Office of The Surgeon General (OTSG) tasked IDA with developing human response models for five prospective chemical agents. The models are intended to be placed in Allied Medical Publication 7.5(A) (AMedP-7.5), which will be the doctrinal replacement of Allied Medical Publication 8(C): NATO Planning Guide for the Estimation of CBRN Casualties (AMedP-8(C)), and is currently in development at IDA, also in support of OTSG.The five agents considered in this document are ammonia, tabun, soman, cyclosarin, and lewisite. For each agent, the authors propose or use existing toxicity and lethality estimates, and describe the progression of injury over time and outcome for a person who received no medical treatment. A separate model that includes the effects of medical treatment is also discussed and derived. The work described in this document is based on an extensive review of available literature, including experimental animal data, human case reports, and human disease outbreak reports.

15. SUBJECT TERMS

casualty estimation, CBRN, chemical, CWA, ammonia, tabun, soman, cyclosarin, lewisite, human response

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